	L #	Hits	Search Text	DBs	Time Stamp
1	L1	116	hbx	USPAT; US-PGPUB	2003/07/08 09:44
2	L2	362	(hepatitis adj b adj virus or hbv) near4 inhibit$8	USPAT; US-PGPUB	2003/07/08 09:45
3	L3	15	1 and 2	USPAT; US-PGPUB	2003/07/08 09:45
4	L4	6	hbx near4 inhibit$8	USPAT; US-PGPUB	2003/07/08 10:44
5	L5	7091	src	USPAT; US-PGPUB	2003/07/08 10:46
6	L6	665867	activat$8	USPAT; US-PGPUB	2003/07/08 10:46
7	L7	201531	upstream	USPAT; US-PGPUB	2003/07/08 10:47
8	L8	2769	6 near5 7	USPAT; US-PGPUB	2003/07/08 10:47
9	L9	19	8 same 5	USPAT; US-PGPUB	2003/07/08 10:47
10	L10	61	5 same 6 same 7	USPAT; US-PGPUB	2003/07/08 10:53
11	L11	221	5 near2 (activator$1 or activation)	USPAT; US-PGPUB	2003/07/08 11:17
12	L12	2937	hbv or hbx	USPAT; US-PGPUB	2003/07/08 11:17
13	L13	9	11 and 12	USPAT; US-PGPUB	2003/07/08 11:18
14	L14	529	5 near5 6	USPAT; US-PGPUB	2003/07/08 11:38
15	L15	29	12 and 14	USPAT; US-PGPUB	2003/07/08 11:38
16	L16	8317	cyclosporin or csa	USPAT; US-PGPUB	2003/07/08 12:10
17	L17	182	16 and 12	USPAT; US-PGPUB	2003/07/08 12:13
18	L18	1	16 same 12	USPAT; US-PGPUB	2003/07/08 12:10
19	L19	304	bapta or cgp37157	USPAT; US-PGPUB	2003/07/08 12:13
20	L20	5	19 and 12	USPAT; US-PGPUB	2003/07/08 12:13

	L #	Hits	Search Text	DBs	Time Stamp
1	L1	116	hbx	USPAT; US-PGPUB	2003/07/08 09:44
2	L2	362	(hepatitis adj b adj virus or hbv) near4 inhibit$8	USPAT; US-PGPUB	2003/07/08 09:45
3	L3	15	1 and 2	USPAT; US-PGPUB	2003/07/08 09:45

PGPUB-DOCUMENT-NUMBER: 20030119724

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030119724 A1

TITLE: Ligands to enhance cellular uptake of biomolecules

PUBLICATION-DATE: June 26, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Ts`o, Paul O.P.	Ellicott City	MD	US	
Duff, Robert	York	PA	US	
Zhou, Yuanzhong	Columbia	MD	US	
Deamond, Scott	Baltimore	MD	US	
Roby, Clinton	Baltimore	MD	US	

APPL-NO: 09/ 888164

DATE FILED: June 22, 2001

RELATED-US-APPL-DATA:

child 09888164 A1 20010622

parent continuation-of 09282455 19990331 US ABANDONED

child 09282455 19990331 US

parent continuation-in-part-of 08755062 19961122 US GRANTED

parent-patent 5994517 US

non-provisional-of-provisional 60007480 19951122 US

US-CL-CURRENT: 514/8, 530/391.1 , 530/395

ABSTRACT:

The present invention relates to the design and synthesis of homogeneous A-L-P constructs, which contain a hepatic ligand to direct an oligomer or "payload" to a hepatocyte intracellularly via a receptor-mediated, ligand-directed pathway.

[0001] This is a continuation-in-part of U.S. Ser. No. 08/755,062, filed Nov. 22, 1996.

---------- KWIC ---------

Detail Description Paragraph - DETX (16):

[0087] In order to assess the biological effects of this enhanced, cell specific delivery, the integrated hepatitis B viral (HBV) genome was targeted by liver specific neoglycoconjugates in a series of in vitro experiments. HBV is a small enveloped hepadavirus (Tiollais et al., (1985), Nature, 317:489-495) that is both a major cause of acute and chronic hepatitis, as well as hepatocellular carcinoma. This virus has a sweeping scope, infecting more than 200 million persons worldwide. The molecular biology of HBV replication has been well characterized and an in vitro model system of hepatoma cells possessing asialoglycoprotein receptors and stably transfected with HBV (Hep G2 2.2.15) has been established (Sells et al., (1987), Proc. Natl. Acad. Sci., 84:1005-1009; Korba and Milman, (1992), Antiviral Res., 19:55-70). Under defined culture conditions, these cells secrete Dane particles into the cell culture media. These particles have been shown to be comprised of a protein coat expressing hepatitis B surface antigen (HBsAG) and a viral DNA core (virion DNA), both of which can be easily assayed in vitro. The corresponding mRNA for these HBV components has been proven to be amenable to modulation by phosphorothioate antisense oligomers (ps-oligomer) (Korba and Gerin, (1995), Antiviral Res., 28:225-242); Goodarzi et al., (1990), J. Gen. Virology, 71:3021-3025); Offensperger et al., (1995), Intervirology, 38:113-119). Recently, enhanced **inhibition of HBV** replication in transfected liver cells has been demonstrated in vitro by ps-oligomers non-covalently conjugated to DNA carrier systems specific for the asialoglycoprotein receptor (Wu and Wu, (1992), J. Biol. Chem., 267:12436-12439); Madon and Blum, (1996), Hepatology, 24:474-481; Yao et al., (1996), Acta. Virologica, 40:35-39).

Detail Description Paragraph - DETX (144):

[0199] Methods: The three therapeutic neoglycoconjugates utilized in this study were synthesized by conjugation of the following ps-oligomers, previously shown to **inhibit HBV** replication in vitro (Korba and Gerin, 1995, supra), to the liver specific ligand YEE(ahGalNAc).sub.3: (1) 5'GTTCTCCATGTTCAG3' which targets the translation initiation site of the surface antigen gene (sa-gene), (2) 5'TTTATAAGGGTCGATGTCCAT3' which targets the translational initiation site of the core gene (c-gene) and overlaps the HBV polyadenylation site and (3) 5'AAAGCCACCCAAGGCA3' which targets the unpaired loop of the encapsidation site of the HBV pregenome (e-site). The base sequence used to synthesize the oligomers for this study was a HBV subtype ayw (Galibert, et. al., (1979), Nature (London), 281:646-650), the same subtype expressed in vitro by HepG2 2.2.15 (Acs et al., (1987), Proc. Natl. Acad. Sci., 84:4641-4644. In addition, two additional ps-oligomers, which are non-complementary to the HBV genome, NG4: .sup.5'TGAGCTATGCACATTCAGATTT.sup.3' and NG5: .sup.5'TCCAATTAGATCAG.sup.3', were prepared as controls to assay for non-specific effects of the ps-neoglycoconjugates.

Detail Description Table CWU - DETL (1):

1TABLE A Hepatitis Viruses Targeted Site Sequence (5'to 3') Hepatitis B Virus (HBV) **HBx** gene TTGGCAGCACACCCTAGCAGCC (SEQ. ID NO.:1) ATGGA HBV surface antigen (S gene) Cap site/ GATGACTGTCTCTTA (SEQ. ID NO.:2) SPII Inside/ AGGAGATTGACGAGA (SEQ. ID NO.:3) pre-S2 Initiator/ GTTCTCCATGTTCGG (SEQ. ID NO.:4) gene S Initiator/ TCTCCATGTTCG (SEQ. ID NO.:5) gene S

Inside I/ GAATCCTGATGTAAT (SEQ. ID NO.:6) gene S Inside II/ AACATGAGGGAAACA (SEQ. ID NO.:7) gene S PreS1 open reading frame HBV core antigen (C gene) Sequence (5'to 3') Hepatitis C Virus (HCV) TFCTCATGGTGCACGGTCTACGA (SEQ. ID NO.:8) CTTTCGCGACCCAACACTAC (SEQ. ID NO.:9) CATGATGCACGGTCTACGAGA (SEQ. ID
NO.:10) GCCTTTCGCGACCCAACACT (SEQ. ID NO.:11) GCCTTTCGCGACCCAAC (SEQ. ID
NO.:12) GCCTTTCGCGACCCAAC (SEQ. ID NO.:13) GTGCTCATGGTGCACGGTCT (SEQ. ID
NO.:14) GTGCTCATGGTGCACG (SEQ. ID NO.:15) CTGCTCATGGTGCACGGTCT (SEQ. ID NO.:16) Hepatitis D Virus (HDV) GCGGCAGTCCTCAGT (SEQ. ID NO.:17) CTCGGCTAGAGGCGG (SEQ. ID NO.:18) CTCGGACCGGCTCAT (SEQ. ID NO.:19) TCTTCCGAGGTCCGG (SEQ. ID NO.:20) ATATCCTATGGAAATCC (SEQ. ID NO.:21) TGAGTGGAAACCCGC (SEQ. ID NO.:22) ATTTGCAAGTCAGGATT. (SEQ. ID NO.:23)

PGPUB-DOCUMENT-NUMBER: 20030032596

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030032596 A1

TITLE: Inhibition of the Src kinase family pathway as a method of treating HBV infection and hepatocellular carcinoma

PUBLICATION-DATE: February 13, 2003

US-CL-CURRENT: 514/12, 514/262.1 , 514/44

APPL-NO: 10/ 196344

DATE FILED: July 15, 2002

RELATED-US-APPL-DATA:

child 10196344 A1 20020715

parent continuation-of 08874430 19970613 US GRANTED

parent-patent 6420338 US

US-PAT-NO: 6465246

DOCUMENT-IDENTIFIER: US 6465246 B1

TITLE: Oncogene- or virus-controlled expression systems

DATE-ISSUED: October 15, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Mueller; Rolf	Marburg	N/A	N/A	DE
Sedlacek; Hans-Harald	Marburg	N/A	N/A	DE

APPL-NO: 09/ 196099

DATE FILED: November 20, 1998

PARENT-CASE:

INFORMATION ON RELATED APPLICATIONS

The present application claims the priority benefit, under 35 U.S.C. .sctn.119, of Federal Republic of Germany Application No. 19751587.8, filed Nov. 21, 1997.

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
DE	197 51 587	November 21, 1997

US-CL-CURRENT: 435/320.1, 435/325 , 435/375 , 435/69.1 , 435/69.7 , 435/91.1 , 435/91.4 , 530/352 , 530/358 , 536/23.1 , 536/23.4 , 536/23.5 , 536/23.72

ABSTRACT:

Nucleic acid constructs for expressing an effector gene, with the nucleic acid construct comprising a promoter I (component a) which controls the expression of a transcription factor gene (component b), a transcription factor gene (component b), a promoter II (component c) to which the gene product of the transcription factor gene binds and which controls the expression of an effector gene (component d), and effector gene (component d), wherein the activity of the gene product of the transcription factor gene depends on one or more cellular regulatory proteins which bind to this gene product and affect its activity, and isolated cells containing the nucleic acid constructs, can be used for preparing a drug for treating diseases and in methods of treating diseases.

2 Claims, 3 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 1

--------- KWIC ---------

Detailed Description Paragraph Table - DETL (2):

Component b.sub.2) Regulatory (viral binding protein having a binding sequence protein for the regulatory protein) p53 IE 84 of CMV (Speir et al., Science 265, 391 (1994) E1B (55 Kd) of AV (Sarnow et al., Cell 28, 387 (1982); Lin et al., Cold Spring Harbor Symp. On Quantitative Biol. LIX, 215 (1995)) EBNA-5 of EBV (Szekely et al., PNAs USA 90, 5455 (1993)) BHFR1 of EBV (Theodorakis et al., Oncogene 12, 1707 (1996)) E6 of HPV-16 or -18 (Dyson et al., Science 243, 934 (1989); Howes et al., Genes Dev. 8, 1300 (1994)) **HBX** protein of HBV (Wang et al., PNAS USA 91, 2230 (1994)) T antigen of SV40 (Lane et al., Nature 278, 261 (1979); Linzer et al., Cell 17, 43 (1979)) PRb E1A of AV (Nevins Science 258, 424 (1992)) EBNA-2 of EBV EBNA-1 or -5 of EBV E7 of HPV T antigen of SV40 p130 E1A of AV (Li et al., Genes Dev. 7, 2366 (1993)) CBF-1 (RBP-JK) EBNA-2 of EBV (Zimber-Strobl et al., EMBO J. 13, 4973 (1994)) NF-Kappa B Tax of HIV (Suzuki et al., Oncogene 9, 3099 (1994)) Lyn-tyrosine kinase LMP-1 of EBV LMP-2A or LMP-2B of EBV Bak E1B (16 Kd) of AV (Farrow et al., Nature 374, 731 (1995)) Bax E1B (19 kD) of Av (Han et al., Genes Dev. 10, 461 (1996))

Other Reference Publication - OREF (125):

Wang, Xin Wei et al., **Hepatitis B virus X protein inhibits** p53 sequence-specific DNA binding, transcriptional activity, and association with transcription factor ERCC3. Proc. Natl. Acad. Sci. USA, vol. 91; pp. 2230-2234 (1994).

	L #	Hits	Search Text	DBs	Time Stamp
1	L1	116	hbx	USPAT; US-PGPUB	2003/07/08 09:44
2	L2	362	(hepatitis adj b adj virus or hbv) near4 inhibit$8	USPAT; US-PGPUB	2003/07/08 09:45
3	L3	15	1 and 2	USPAT; US-PGPUB	2003/07/08 09:45
4	L4	6	hbx near4 inhibit$8	USPAT; US-PGPUB	2003/07/08 10:44

PGPUB-DOCUMENT-NUMBER: 20030032596

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030032596 A1

TITLE: Inhibition of the Src kinase family pathway as a method of treating HBV infection and hepatocellular carcinoma

PUBLICATION-DATE: February 13, 2003

US-CL-CURRENT: 514/12, 514/262.1 , 514/44

APPL-NO: 10/ 196344

DATE FILED: July 15, 2002

RELATED-US-APPL-DATA:

child 10196344 A1 20020715

parent continuation-of 08874430 19970613 US GRANTED

parent-patent 6420338 US

	L #	Hits	Search Text	DBs	Time Stamp
1	L1	116	hbx	USPAT; US-PGPUB	2003/07/08 09:44
2	L2	362	(hepatitis adj b adj virus or hbv) near4 inhibit$8	USPAT; US-PGPUB	2003/07/08 09:45
3	L3	15	1 and 2	USPAT; US-PGPUB	2003/07/08 09:45
4	L4	6	hbx near4 inhibit$8	USPAT; US-PGPUB	2003/07/08 10:44
5	L5	7091	src	USPAT; US-PGPUB	2003/07/08 10:46
6	L6	665867	activat$8	USPAT; US-PGPUB	2003/07/08 10:46
7	L7	201531	upstream	USPAT; US-PGPUB	2003/07/08 10:47
8	L8	2769	6 near5 7	USPAT; US-PGPUB	2003/07/08 10:47
9	L9	19	8 same 5	USPAT; US-PGPUB	2003/07/08 10:47

PGPUB-DOCUMENT-NUMBER: 20030124540

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030124540 A1

TITLE: Interventions to mimic the effects of calorie restriction

PUBLICATION-DATE: July 3, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Spindler, Stephen R.	Riverside	CA	US	

APPL-NO: 10/ 056749

DATE FILED: January 22, 2002

RELATED-US-APPL-DATA:

child 10056749 A1 20020122

parent continuation-of 09648642 20000825 US GRANTED

parent-patent 6406853 US

US-CL-CURRENT: 435/6, 435/4

ABSTRACT:

Long term calorie restriction has the benefit of increasing life span. Methods to screen interventions that mimic the effects of calorie restriction are disclosed. Extensive analysis of genes for which expression is statistically different between control and calorie restricted animals has demonstrated that specific genes are preferentially expressed during calorie restriction. Screening for interventions which produce the same expression profile will provide interventions that increase life span. In a further aspect, it has been discovered that test animals on a calorie restricted diet for a relatively short time have a similar gene expression profile to test animals which have been on a long term calorie restricted diet.

---------- KWIC ---------

Detail Description Table CWU - DETL (12):

10TABLE 10 mR: VAs decreased by age and returned to control levels by LT-CR GenBank Phenotype Immune System M30903 B lymphocyte kinase (Blk); src-family protein tyrosine kinase; plays important role in B-cell development/activation and immune responses; B-lineage cells U43384 Cytochrome

b-245, beta polypeptide (Cybb, cytochrome b558); integral component of the microbicidal oxidase electron transport chain of phagocytic cells, respiratory burst oxidase; phagocytes U10871 Mitogen activated protein kinase 14 (Mapk14); signal transduction, stimulate phosphorylation of transcription factors; major **upstream activator** of MAPKAP kinas 2; hematopoietic stem cells 222649 Myeloproliferative leukemia virus oncogene (Mpl); Member of hematopoietic cytokine receptor family, cell cycle regulator, induces proliferation and differentiation of hematopoietic cell lines; hematopoietic precursor cells, platelets and megakaryocytes Y07521 Potassium voltage gated channel, Shaw-related subfamily member 1 (Kcncl) potassium channels with properties of delayed rectifiers; nervous system, skeletal system, T lymphocytes U87456 Flavin-containing monooxygenase 1 (Fmol); xenobiotic metabolism; highly expressed in liver, lung, kidney, lower expressed in heart, spleen, testis, brain U40189 Pancreatic polypeptide receptor 1 (Ppyrl), neuropeptide Y receptor, peptide Y receptor; G-protein-coupled receptor; liver, gastrointestinal tract, prostate, neurons endocrine cells Neuron Specific U16297 Cytochrome b-561 (Cyb561); electron transfer protein unique to neuroendocrin secretory vesicles; vectoral transmembrane electron transport; brain D50032 Trans-golgi network protein 2 (Ttgn2); integral membrane protein localized to the trans-Golgi network; involved in the budding of exocytic transport vesicles; brain neurons Liver Specific/Ubiquitous D82019 Basigin (Bsg), CD147, neurothelin; membrane glycoprotein, immunoglobulin superfamily, homology to MHCs, acts as an adhesion molecule or a receptor, near: network formation and tumor progression; embryo, liver and other organs L38990 Glucokinase (Gk), key glycolytic enzyme; liver U50631 Heat-responsive protein 12 (Hrsp 12); heat-responsive, phosphorylated protein sequence simularity to Hsp70; liver, kidney U39818 Tuberous sclerosis 2 (Tsc2); mutationally inactivated in some families with tuberoi sclerosis; encodes a large, membrane-associated GTPase activating protein (GA tuberlin); may have a key role in the regulation of cellular growth; ubiquitous

PGPUB-DOCUMENT-NUMBER: 20030078406

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030078406 A1

TITLE: Methods and compositions for DRM, a secreted protein with cell growth inhibiting activity

PUBLICATION-DATE: April 24, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Blair, Donald G.	Frederick	MD	US	
Clausen, Peter A.	Frederick	MD	US	
Topol, Lilia Z.	Frederick	MD	US	
Marx, Maria	L'Hay Les Roses		FR	
Calothy, Georges	Orsay		FR	

APPL-NO: 10/ 033717

DATE FILED: December 27, 2001

RELATED-US-APPL-DATA:

child 10033717 A1 20011227

parent continuation-of 09444066 19991119 US ABANDONED

child 09444066 19991119 US

parent continuation-of 09277407 19990326 US ABANDONED

non-provisional-of-provisional 60079440 19980326 US

US-CL-CURRENT: 536/23.5, 435/320.1 , 435/325 , 435/69.1 , 530/350

ABSTRACT:

The present invention provides an isolated nucleic acid encoding DRM protein, an isolated DRM polypeptide, and a fusion polypeptide comprising a DRM protein and a green fluorescent protein. The present invention also provides a method of arresting the growth of a cell, comprising administering to the cell an effective amount of DRM protein or an active fragment thereof; a method of inhibiting tumor cell growth, comprising administering to a tumor cell an effective amount of DRM protein or an active fragment thereof; and a method of treating a hyperproliferative cell disorder in a subject diagnosed with a hyperproliferative cell disorder, comprising administering to the subject an effective amount of DRM protein or an active fragment thereof, in a pharmaceutically acceptable carrier. In addition, the present invention provides a method of arresting growth of a cell, comprising administering to

the cell an effective amount of a nucleic acid encoding a DRM protein or an active fragment thereof, a method of inhibiting tumor cell growth, comprising administering to a tumor cell an effective amount of a nucleic acid encoding a DRM protein or an active fragment thereof; and a method of treating a hyperproliferative cell disorder in a subject diagnosed with a hyperproliferative cell disorder, comprising administering to a cell of the subject, in a pharmaceutically acceptable carrier, an effective amount of a nucleic acid encoding a DRM protein or an active fragment thereof, under conditions whereby the nucleic acid is expressed in the subject's cell.

[0001] This application claims priority to U.S. patent application Ser. No. 09/277,407, filed on Mar. 26, 1999, now abandoned, which claims priority to provisional application Serial No. 60/079,440 filed on Mar. 26, 1998, both of which are hereby incorporated herein by reference in their entirety.

---------- KWIC ---------

Detail Description Paragraph - DETX (31):

[0123] The characterization of a flat (non-transformed) revertant cell line, F-1, which was isolated from rat fibroblasts (DTM) transformed by the serine/threonine kinase oncogene mos has been previously reported (41). F-1 cells express high levels of v-mos-specific RNA and kinase activity, but fail to express characteristic transformed properties, including colony formation in soft agar and tumor formation in nude mice. Moreover, the revertants are resistant to re-transformation by v-mos and v-raf while they can be efficiently transformed by v-ras and, with a somewhat lower efficiency, v-**src**. The reversion and resistance to re-transformation correlated with the failure of the serine/threonine kinase oncogenes v-mos and v-raf to activate the MAP kinase pathway due to their inability to activate MEK-1 or MEK-2, the immediate **upstream activators** of MAP kinase.

PGPUB-DOCUMENT-NUMBER: 20030077284

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030077284 A1

TITLE: Product and method for treatment of conditions associated with receptor-desensitization

PUBLICATION-DATE: April 24, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Vilen, Barbara J.	Chapel Hill	NC	US	
Cambier, John C.	Denver	CO	US	

APPL-NO: 10/ 218670

DATE FILED: August 13, 2002

RELATED-US-APPL-DATA:

child 10218670 A1 20020813

parent continuation-of 09513024 20000225 US GRANTED

parent-patent 6503509 US

non-provisional-of-provisional 60121954 19990225 US

US-CL-CURRENT: 424/153.1

ABSTRACT:

Particular members of the multisubunit immune recognition receptor (MIRR) family of receptors, specifically, the B cell antigen receptor (BCR), the pre-B cell receptor (pre-BCR), the pro-B cell receptor (pro-BCR), Ig Fc receptors (FcR), and NK receptors, can be physically uncoupled from their associated transducers. The invention describes regulatory compounds and methods for mimicking such dissociation/destabilization for the purposes of receptor desensitization and for treatment of conditions in which receptor desensitization or alternatively, enhanced or prolonged receptor sensitization, is desirable. Compounds and methods for enhancing or prolonging receptor sensitization are also disclosed, as are methods for identifying regulatory compounds suitable for use in the present methods.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. .sctn. 119(e) from U.S. Provisional Application Serial No. 60/121,954, filed Feb. 25, 1999, entitled "Product and Method for Treatment of Conditions Associated with

Receptor-Desensitization." The entire disclosure of U.S. Provisional Application Serial No. 60/121,954 is incorporated herein by reference in its entirety.

---------- KWIC ---------

Detail Description Paragraph - DETX (76):

[0110] Previous studies of desensitized cells suggested that the defect in BCR signaling lies **upstream of src-family kinase activation,** possibly at the level of the receptor (Vilen et al., 1997). To address changes in BCR structure under conditions of receptor desensitization, the .mu.-heavy chain, Ig-.alpha. or Ig-.beta. were immunoprecipitated from desensitized K46.mu. cell lysates and the coprecipitated BCR components were quantitated. Briefly, a comparative analysis of mIg-Ig-.alpha./Ig-.beta. association in unstimulated K46.mu. cells, cells stimulated 1 hour with NP.sub.7BSA (500 mg/5.times.10.sup.6 cells/ml) or cells stimulated 1 hour with biotinylated b-7-6 (10 .mu.g/5.times.10.sup.6/ml) was performed. Biotinylated b-7-6 was prebound to unstimulated cells (10 .mu.g/5.times.10.sup.6 cells/ml) for 2 minutes at 4.degree. C. prior to lysis. FIG. 1 shows the results of the analysis as follows: Panel 1: Lanes 1 and 2 represent IgM and Ig-.alpha. immunoblots of anti-.mu. immunoprecipitates. Panel 2: Lanes 3 and 4 represent IgM, Ig-.beta. and Ig-.alpha. immunoblots of anti-Ig-.beta. immunoprecipitates. Panel 3: Lanes 5 and 6 represent IgM and Ig-.alpha. immunoblots of Ig-.alpha. immunoprecipitates. Panel 4: Lanes 7 and 8 represent IgM and Ig-.alpha. immunoblots of streptavidin immunoprecipitates.

PGPUB-DOCUMENT-NUMBER: 20030073163

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030073163 A1

TITLE: Libraries of expressible gene sequences

PUBLICATION-DATE: April 17, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Fernandez, Joseph Manuel	Carlsbad	CA	US	
Heyman, John Alastair	Cardiff-by-the-Sea	CA	US	
Hoeffler, James Paul	Carlsbad	CA	US	

APPL-NO: 10/ 003021

DATE FILED: November 14, 2001

RELATED-US-APPL-DATA:

child 10003021 A1 20011114

parent continuation-of 09285386 19990402 US PENDING

non-provisional-of-provisional 60096981 19980818 US

non-provisional-of-provisional 60080626 19980403 US

US-CL-CURRENT: 435/69.1, 435/183 , 435/193 , 435/320.1 , 435/325 , 435/6 , 536/23.2

ABSTRACT:

The invention described herein comprises libraries of expressible gene sequences. Such gene sequences are contained on plasmid vectors designed to endow the expressed proteins with a number of useful features such as affinity purification tags, epitope tags, and the like. The expression vectors containing such gene sequences can be used to transfect cells for the production of recombinant proteins. A further aspect of the invention comprises methods of identifying binding partners for the products of such expressible gene sequences.

RELATED APPLICATIONS

[0001] This application relies for priority on U.S. Provisional Application No. 60/080,626, filed Apr. 3, 1998, and U.S. Provisional Application No. 60/096,981, filed Aug. 18, 1998, each of which is hereby incorporated herein in its entirety.

---------- KWIC ---------

Detail Description Table CWU - DETL (19):

M221 E6 YLR142W proline oxidase (52.47/60) M84 C2 YLR144C Identified as an activity necessary for actin polymerization in permeabilized cells (85.72/90) M79 E4 YLR009W (22/32) M219 D4 YLR010C (17./6330) M219 D5 YLR011W (21.1/230) M219 D1 YLR015W (55.66/64) M219 D2 YLR016C (22.47/40) M219 D3 YLR017W Protein that regulates ADH2 gene expression (37.18/48) M219 E5 YLR019W (43.78/50) M219 E8 YLR022C (27.53/38) M80 A6 YLR026C Sed5p is a t-SNARE (soluble NSF attachment protein receptor) required in ER to Golgi transport. (37.43/25) M219 F5 YLR027C aspartate aminotransferase cytosolic (47.55/50) M79 F8 YLR029C Ribosomal protein RPL13A (YL10A) (rat L15) (22.47/30) M219 F8 YLR030W (29.04/40) M80 C2 YLR031W (20.57/32) M219 F3 YLR033W (55.33/55) M219 F6 YLR036C (22.46/33) M80 B10 YLR037C (13.67/13) M223 E1 YLR040C (24.67/38) M82 C6 YLR043C thioredoxin (11.46/12) M81 F7 YLR044C pyruvate decarboxylase (61.96/62) M82 D6 YLR051C (23.90/30) M222 G7 YLR053C (11.91/22) M82 C10 YLR054C (56.45/56) M223 B1 YLR055C transcription factor (66.35/70) M81 D2 YLR056W C-5 sterol desaturase (40.36/55) M81 H3 YLR057W (93.5/98) M81 D5 YLR058C serine hydroxymethyltransfe rase (51.62/55) M82 E6 YLR059C (29.62/30) M81 H7 YLR060W Phenylalanyl-tRNA synthetase alpha subunit cytoplasmic (65.56/65) M82 H8 YLR061W 402-755 (13.42/28) M222 A5 YLR066W signal peptidase subunit (20.45/34) M222 H3 YLR073C (22.03/34) M81 E5 YLR074C (18.39/28) M81 E5 YLR074C (18.39/28) M222 A6 YLR075W Ubiquinol- cytochrome C reductase complex subunit VI requiring protein (24.42/33) M222 A6 YLR075W Ubiquinol-cytochrome C reductase complex subunit VI requiring protein (24.42/33) M82 A8 YLR076C (15.43/16) M222 H7 YLR077W (64.24/67) M223 G5 YLR077W (64.24/60) M81 D1 YLR079W P40 inhibitor of Cdc28p-Clb5 protein kinase complex (31.45/50) M223 G3 YLR082C Smc4 protein member of SMC family (43.25/55) M222 B6 YLR083C integral membrane protein.backslash.p24a protein (73.40/90) M222 B4 YLR089C (65.25/65) M222 B4 YLR089C (65.25/65) M81 G5 YLR090W Homolog of E. coli DnaJ closely related to Ydj1p (50.6/60) M81 H6 YLR091W (32.34/40) M81 H6 YLR091W (32.34/40) M222 B8 YLR093C (27.64/39) M223 H2 YLR097C (37.87/52) M81 H5 YLR098C DNA binding activator (71.31/75) M222 D6 YLR099C (43.47/48) M82 C8 YLR100W (38.38/?) M82 C8 YLR100W (38.38/?) M81 A11 YLR102C (29.28/45) M82 F1 YLR103C omosomal DNA replication initiation protein (71.53/?) M222 E6 YLR107W (44.55/48) M222 D8 YLR109W (19.47/38) M81 G4 YLR113W mitogen-activated protein kinase (MAP kinase) (47.96/60) M81 A6 YLR114C (84.07/100) M81 A6 YLR114C (84.07/100) M223 D1 YLR119W suppressor of rnal-1 mutation (23.54/33) M222 D7 YLR124W (12.65/16) M222 F8 YLR125W (15.07/40) M82 A2 YLR127C APC (anaphase promoting complex) component (93.86/94) M82 D7 YLR131C activator of CUP1 expression (84.73/40) M222 E7 YLR132C (31.93/40) M221 A3 YLR137W (40.48/52) M84 C6 YLR139C (70.76/70) M86 G9 YLR141W **Upstream activation** factor subunit (40.04/55) M221 E6 YLR142W proline oxidase (52.47/60) M84 C2 YLR144C Identified as an activity necessary for actin polymerization in permeabilized cells (85.72/90) M221 F6 YLR150W (30.14/42) M255 H6 YLR151C (37.43/52) M84 G3 YLR153C acetyl-coenzyme A synthetase (75.16/75) M221 G4 YLR155C nitrogen catabolite-regulated cell-wall L- asparaginase II (39.85/50) M221 A2 YLR160C nitrogen catabolite- regulated cell-wall L- asparaginase II (39.85/50) M84 A8 YLR164W (18.59/19) M221 B1 YLR167W ubiquitin (16.83/16) M221 B2 YLR168C

(25.33/35) M86 G8 YLR172C S-adenosylmethionine (AdoMet)-dependent methyltransferase of diphthamide biosynthesis (33.03/40) M224 F1 YLR175W major low affinity 55 kDa Centromere.backslash./microtub ule binding protein (53.24/60) M221 C2 YLR176C (89.24/96) M86 H5 YLR178C suppressor of cdc25 (24.12/38) M221 H4 YLR179C (22.14/33) M221 F5 YLR180W S-adenosylmethionine synthetase (42.13/48) M221 E4 YLR186W (27.83/36) M84 A7 YLR187W (112.97/114) M84 D8 YLR188W ATP-binding cassette (ABC) transporter family member (76.56/76) M84 H9 YLR189C (131.81/?) M84 D11 YLR190W (54.12/70) M84 G1 YLR191W Peroxisomal membrane protein that contains **Src** homology 3 (SH3) domain (42.57/45) M221 F3 YLR193C (19.38/30) M84 B7 YLR195C N-myristoyl transferase (50.08/32) M84 A10 YLR197W homology to microtubule binding proteins and to X90565_5.cds (55.55/55) M221 D1 YLR199C (24.23/36) M221 E2 YLR200W Polypeptide 6 of a Yeast Non-native Actin Binding Complex homolog of a component of the bovine NABC complex (12.65/18) M84 D4 YLR201C (28.63/40) M84 C7 YLR203C Protein involved in maturation of COX1 and COB mRNA (47.99/48)

US-PAT-NO: 6503509

DOCUMENT-IDENTIFIER: US 6503509 B1

TITLE: Method for receptor desensitization

DATE-ISSUED: January 7, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Vilen; Barbara J.	Chapel Hill	NC	N/A	N/A
Cambier; John C.	Denver	CO	N/A	N/A

APPL-NO: 09/ 513024

DATE FILED: February 25, 2000

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. .sctn. 119(e) from U.S. Provisional Application Ser. No. 60/121,954, filed Feb. 25, 1999, entitled "Product and Method for Treatment of Conditions Associated with Receptor-Desensitization." The entire disclosure of U.S. Provisional Application Ser. No. 60/121,954 is incorporated herein by reference in its entirety.

US-CL-CURRENT: 424/153.1, 424/130.1 , 424/136.1 , 424/137.1 , 424/141.1 , 424/143.1 , 424/144.1 , 424/152.1 , 424/172.1 , 424/173.1 , 435/70.21 , 514/2 , 514/885 , 530/387.1 , 530/387.3 , 530/388.1 , 530/388.2 , 530/388.22 , 530/388.7 , 530/388.73 , 530/389.1 , 530/389.6

ABSTRACT:

Particular members of the multisubunit immune recognition receptor (MIRR) family of receptors, specifically, the B cell antigen receptor (BCR), the pre-B cell receptor (pre-BCR), the pro-B cell receptor (pro-BCR), Ig Fc receptors (FcR), and NK receptors, can be physically uncoupled from their associated transducers. The invention describes regulatory compounds and methods for mimicking such dissociation/destabilization for the purposes of receptor desensitization and for treatment of conditions in which receptor desensitization or alternatively, enhanced or prolonged receptor sensitization, is desirable. Compounds and methods for enhancing or prolonging receptor sensitization are also disclosed, as are methods for identifying regulatory compounds suitable for use in the present methods.

18 Claims, 15 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 11

---------- KWIC ---------

Detailed Description Text - DETX (76):

Previous studies of desensitized cells suggested that the defect in BCR signaling lies **upstream of src-family kinase activation,** possibly at the level of the receptor (Vilen et al., 1997). To address changes in BCR structure under conditions of receptor desensitization, the .mu.-heavy chain, Ig-.alpha. or Ig-.beta. were immunoprecipitated from desensitized K46.mu. cell lysates and the coprecipitated BCR components were quantitatcd. Briefly, a comparative analysis of mIg-Ig-.alpha./Ig-.beta. association in unstimulated K46.mu. cells, cells stimulated 1 hour with NP.sub.7 BSA (500 mg/5.times.10.sup.6 cells/ml) or cells stimulated 1 hour with biotinylated b-7-6 (10 .mu.g/5.times.10.sup.6 /ml) was performed. Biotinylated b-7-6 was prebound to unstimulated cells (10 .mu.g/5.times.10.sup.6 cells/ml) for 2 minutes at 4.degree. C. prior to lysis. FIG. 1 shows the results of the analysis as follows: Panel 1: Lanes 1 and 2 represent IgM and Ig-.alpha. immunoblots of anti-.mu. immunoprecipitates. Panel 2: Lanes 3 and 4 represent IgM, Ig-.beta. and Ig-.alpha. immunoblots of anti-Ig-.beta. immunoprecipitates. Panel 3: Lanes 5 and 6 represent IgM and Ig-.alpha. immunoblots of Ig-.alpha. immunoprecipitates. Panel 4: Lanes 7 and 8 represent IgM and Ig-.alpha. immunoblots of streptavidin immunoprecipitates.

US-PAT-NO: 6475778

DOCUMENT-IDENTIFIER: US 6475778 B1

TITLE: Differentiation enhancing factors and uses therefor

DATE-ISSUED: November 5, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Roberts; Thomas M.	Cambridge	MA	N/A	N/A
King; Frederick J.	Brookline	MA	N/A	N/A
Harris; David F.	Gales Ferry	CT	N/A	N/A
Hu; Erding	King of Prussia	PA	N/A	N/A
Spiegelman; Bruce	Waban	MA	N/A	N/A
Chan; Joanne	Brookline	MA	N/A	N/A

APPL-NO: 09/ 023905

DATE FILED: February 13, 1998

PARENT-CASE:

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 60/038,191 filed on Feb. 14, 1997, the contents of which are incorporated herein by reference.

US-CL-CURRENT: 435/320.1, 435/325 , 435/455 , 435/69.1 , 536/23.1 , 536/23.5

ABSTRACT:

The present invention relates to novel SH3 domain binding protein, referred to herein a DEF polypeptides. The DEF polypeptides comprise several motifs including a src SH3 consensus binding sequence, four ankyrin repeats, one zinc finger domain and six copies of a proline-rich tandem repeat. DEF polypeptides may function as mediators of SH3 domain-dependent signal transduction pathways and, thus may mediate multiple signaling events such as cellular gene expression, cytoskeletal architecture, protein trafficking and endocytosis, cell adhesion, migration, proliferation and differentiation. Described herein are isolated and antisense nucleic acids molecules, recombinant expression vectors, host cells and non-human transgenic animals containing an insertion or a disruption of the DEF gene. Diagnostic, screening and therapeutic methods utilizing the compositions of the invention are also provided

12 Claims, 37 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 34

---------- KWIC ---------

Detailed Description Text - DETX (129):

The invention also provides for reduction of the mammalian DEF proteins to generate mimetics, e.g. peptide or non-peptide agents, which are able to disrupt binding of a mammalian DEF polypeptide of the present invention with binding proteins or interactors. Thus, such mutagenic techniques as described above are also useful to map the determinants of the DEF proteins which participate in protein-protein interactions involved in, for example, binding of the subject mammalian DEF polypeptide to proteins which may function **upstream (including both activators** and repressors of its activity) or to proteins or nucleic acids which may function downstream of the DEF polypeptide, whether they are positively or negatively regulated by it. To illustrate, the critical residues of a subject DEF polypeptide which are involved in molecular recognition of interactor proteins or molecules upstream or downstream of a DEF (such as, for example, a **src** SH3 binding site, a zinc finger domain, an ankyrin repeat) can be determined and used to generate DEF-derived peptidomimetics which competitively inhibit binding of the authentic DEF protein to that moiety. By employing, for example, scanning mutagenesis to map the amino acid residues of each of the subject DEF proteins which are involved in binding other intracellular proteins, peptidomimetic compounds can be generated which mimic those residues of the DEF protein which facilitate the interaction. Such mimetics may then be used to interfere with the normal function of a DEF protein. For instance, non-hydrolyzable peptide analogs of such residues can be generated using benzodiazepine (e.g., see Freidinger et al. in Peptides: Chemistry and Biology, G. R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), azepine (e.g., see Huffman et al. in Peptides: Chemistry and Biology, G. R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), substituted .gamma. lactam rings (Garvey et al. in Peptides: Chemistry and Biology, G. R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), keto-methylene pseudopeptides (Ewenson et al. (1986) J Med Chem 29:295; and Ewenson et al. in Peptides: Structure and Function (Proceedings of the 9th American Peptide Symposium) Pierce Chemical Co. Rockland, Ill., 1985), b-turn dipeptide cores (Nagai et al. (1985) Tetrahedron Lett 26:647; and Sato et al. (1986) J Chem Soc Perkin Trans 1:1231), and b-aminoalcohols (Gordon et al. (1985) Biochem Biophys Res Commun 126:419; and Dann et al. (1986) Biochem Biophys Res Commun 134:71).

US-PAT-NO: 6469063

DOCUMENT-IDENTIFIER: US 6469063 B1

TITLE: Inhibition of inflammation via inhibition of COX-2 gene transcription

DATE-ISSUED: October 22, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bleich; David	Pasadena	CA	N/A	N/A
Chen; Songyuan	Duarte	CA	N/A	N/A
Han; Xiao	Duarte	CA	N/A	N/A

APPL-NO: 09/ 714889

DATE FILED: November 17, 2000

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is related to provisional application No.60/166,161, filed Nov. 18, 1999, the specification of which is incorporated herein by reference.

US-CL-CURRENT: 514/538, 514/540

ABSTRACT:

The present invention is directed to a method of treating inflammation comprising administering to a subject in need thereof an amount of a caffeic acid derivative sufficient to inhibit the transcription of COX-2. In a preferred embodiment the caffeic acid derivative is a cyanocinnamate, most preferably cinnamamyl-3,4-dihydroxy-.alpha.-cyanocinnamate.

5 Claims, 9 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 9

---------- KWIC ---------

Detailed Description Text - DETX (2):

It has previously been published that 12-HETE, the major 12-LO end product, induces JNK in RIN m5F cells [28]. Furthermore, Herschmann and colleagues demonstrated that v-**src** induces COX-2 gene transcription by activating JNK and

c-jun [29]. These studies demonstrate that c-jun may activate COX-2 gene transcription by binding to the cAMP response element (CRE) in the COX-2 promoter. In the present study it is demonstrated that 12-HETE acts as a specific **upstream agent in activating** COX-2 gene transcription. As seen in FIG. 9, a schematic signaling pathway is depicted that identifies key elements in the pathway leading from cytokine-stimulation to COX-2 gene activation in pancreatic .beta.-cells. Furthermore, since rat tissue does not contain the putative CRE in the COX-2 promoter, it is likely that 12-HETE regulates COX-2 gene transcription through a novel promoter sequence.

	L #	Hits	Search Text	DBs	Time Stamp
1	L1	116	hbx	USPAT; US-PGPUB	2003/07/08 09:44
2	L2	362	(hepatitis adj b adj virus or hbv) near4 inhibit$8	USPAT; US-PGPUB	2003/07/08 09:45
3	L3	15	1 and 2	USPAT; US-PGPUB	2003/07/08 09:45
4	L4	6	hbx near4 inhibit$8	USPAT; US-PGPUB	2003/07/08 10:44
5	L5	7091	src	USPAT; US-PGPUB	2003/07/08 10:46
6	L6	665867	activat$8	USPAT; US-PGPUB	2003/07/08 10:46
7	L7	201531	upstream	USPAT; US-PGPUB	2003/07/08 10:47
8	L8	2769	6 near5 7	USPAT; US-PGPUB	2003/07/08 10:47
9	L9	19	8 same 5	USPAT; US-PGPUB	2003/07/08 10:47
10	L10	61	5 same 6 same 7	USPAT; US-PGPUB	2003/07/08 10:53

PGPUB-DOCUMENT-NUMBER: 20030125265

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030125265 A1

TITLE: Anti-estrogen receptor agents for chemotherapy

PUBLICATION-DATE: July 3, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hung, Mien-Chie	Houston	TX	US	
Lau, Yiu-Keung	Williamsville	NY	US	
Wen, Yong	South San Francisco	CA	US	

APPL-NO: 10/ 142115

DATE FILED: May 9, 2002

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60289658 20010509 US

US-CL-CURRENT: 514/27, 514/456 , 514/680

ABSTRACT:

Methods and compositions regarding the prevention of ER-positive cancer and the treatment of ER-positive HER-2/neu-negative breast cancer are disclosed. Compositions exhibiting both tyrosine kinase inhibitor activity and anti-estrogen receptor activity are useful in the cancer treatment.

[0001] The present application claims priority to U.S. Provisional Patent Application No. 60/289,658, filed May 9, 2001.

---------- KWIC ---------

Detail Description Table CWU - DETL (3):

3TABLE 2 ONCOGENES Gene Source Human Disease Function Growth Factors.sup.1 HST/KS Transfection FGF family member INT-2 MMTV promoter FGF family member Insertion INTI/WNTI MMTV promoter Factor-like Insertion SIS Simian sarcoma PDGF B virus Receptor Tyrosine Kinases.sup.1,2 ERBB/HER Avian Amplified, deleted EGF/TGF.alpha./ erythroblastosis squamous cell amphiregulin/ virus; ALV cancer; hetacellulin promoter glioblastoma receptor insertion; amplified human tumors ERBB-2/NEU/HER-2 Transfected from rat Amplified breast, Regulated by NDF/ Glioblatoms ovarian, gastric heregulin and cancers EGF- related factors FMS SM feline sarcoma CSF-1 receptor virus KIT HZ feline sarcoma MGF/Steel receptor virus hematopoieis TRK Transfection

from NGF (nerve growth human colon factor) receptor cancer MET Transfection from Scatter factor/HGF human receptor osteosarcoma RET Translocations and Sporadic thyroid Orphan receptor Tyr point mutations cancer; kinase familial medullary thyroid cancer; multiple endocrine neoplasias 2A and 2B ROS URII avian sarcoma Orphan receptor Tyr Virus kinase PDGF receptor Translocation Chronic TEL(ETS-like myclomonocytic transcription leukemia factor)/ PDGF receptor gene fusion TGF-.beta.receptor Colon carcinoma mismatch mutation target NONRECEPTOR TYROSINE KINASES.sup.1 ABI. Abelson Mul.V Chronic Interact with RB, myelogenous RNA leukemia polymerase, CRK, translocation CBL with BCR FPS/FES Avian Fujinami SV; GA FeSV LCK Mul.V (murine **Src** family; T cell leukemia signaling; interacts virus) promoter CD4/CD8 T cells insertion **SRC** Avian Rous Membrane- sarcoma associated Tyr Virus kinase with signaling function; **activated** by receptor kinases YES Avian Y73 virus **Src** family; signaling SER/THR PROTEIN KINASES.sup.1 AKT AKT8 murine Regulated by retrovirus PI(3)K?; regulate 70-kd S6 k? MOS Maloney murine SV GVBD; cystostatic factor; MAP kinase kinase PIM-1 Promoter insertion Mouse RAF/MIL 3611 murine SV; Signaling in RAS MH2 pathway avian SV MISCELLANEOUS CELL SURFACE.sup.1 APC Tumor suppressor Colon cancer Interacts with catenins DCC Tumor suppressor Colon cancer CAM domains E-cadherin Candidate tumor Breast cancer Extracellular Suppressor homotypic binding; intracellular interacts with catenins PTC/NBCCS Tumor suppressor Nevoid basal cell 12 transmembrane and cancer domain; signals Drosophilia syndrome (Gorline through Gli homology syndrome) homogue CI to antagonize hedgehog pathway TAN-1 Notch Translocation T-ALI. Signaling? homologue MISCELLANEOUS SIGNALING.sup.1,3 BCL-2 Translocation B-cell lymphoma Apoptosis CBL Mu Cas NS-1 V Tyrosine- phosphorylated RING finger interact Ab1 CRK CT1010 ASV Adapted SH2/SH3 interact Ab1 DPC4 Tumor suppressor Pancreatic cancer TGF-.beta.-related signaling pathway MAS Transfection and Possible angiotensin Tumorigenicity receptor NCK Adaptor SH2/SH3 GUANINE NUCLEOTIDE EXCHANGERS AND BINDING PROTEINS.sup.3,4 BCR Translocated with Exchanger; protein ABL kinase in CML DBL Transfection Exchanger GSP NF-1 Hereditary tumor Tumor suppressor RAS GAP Suppressor neurofibromatosis OST Transfection Exchanger Harvey-Kirsten, N- HaRat SV; Ki Point mutations in Signal cascade RAS RaSV; many Balb-MoMuSV; human tumors Transfection VAV Transfection S112/S113; exchanger NUCLEAR PROTEINS AND TRANSCRIPTION FACTORS.sup.1,5-9 BRCA1 Heritable suppressor Mammary Localization cancer/ovarian unsettled cancer BRCA2 Heritable suppressor Mammary cancer Function unknown ERBA Avian thyroid hormone erythroblastosis receptor Virus (transcription) ETS Avian E26 virus DNA binding EVII MuLV promotor AML Transcription factor Insertion FOS FBI/FBR murine 1 transcription osteosarcoma factor viruses with c-JUN GLI Amplified glioma Glioma Zinc finger; cubitus interruptus homologue is in hedgehog signaling pathway; inhibitory link PTC and hedgehog HMGG/LIM Translocation Lipoma Gene fusions high t(3:12) mobility group t(12:15) HMGI-C (XT- hook) and transcription factor LIM or acidic domain JUN ASV-17 Transcription factor AP-1 with FOS MLL/VHRX + Translocation/fusion Acute myeloid Gene fusion of ELI/MEN ELL with MLL leukemia DNA-Trithorax-like gene binding and methyl transferase MLL with ELI RNA pol II elongation factor MYB Avian DNA binding myeloblastosis Virus MYC Avian MC29; Burkitt's lymphoma DNA binding with Translocation B- MAX partner; cell cyclin Lymphomas; regulation; interact promoter RB?; regulate Insertion avian apoptosis? leukosis Virus N-MYC Amplified Neuroblastoma L-MYC Lung cancer REL Avian NF-.kappa.B family transcription factor Retriculoendothelio sis Virus SKI Avian SKV770 Transcription factor

Retrovirus VHL Heritable suppressor Von Hippel-Landau Negative regulator syndrome or elongin; transcriptional elongation complex WT-1 Wilm's tumor Transcription factor CELL CYCLE/DNA DAMAGE RESPONSE.sup.10-21 ATM Hereditary disorder.Ataxia- Protein/lipid kinase telangiectasia homology; DNA damage response **upstream** in P53

PGPUB-DOCUMENT-NUMBER: 20030124540

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030124540 A1

TITLE: Interventions to mimic the effects of calorie restriction

PUBLICATION-DATE: July 3, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Spindler, Stephen R.	Riverside	CA	US	

APPL-NO: 10/ 056749

DATE FILED: January 22, 2002

RELATED-US-APPL-DATA:

child 10056749 A1 20020122

parent continuation-of 09648642 20000825 US GRANTED

parent-patent 6406853 US

US-CL-CURRENT: 435/6, 435/4

ABSTRACT:

Long term calorie restriction has the benefit of increasing life span. Methods to screen interventions that mimic the effects of calorie restriction are disclosed. Extensive analysis of genes for which expression is statistically different between control and calorie restricted animals has demonstrated that specific genes are preferentially expressed during calorie restriction. Screening for interventions which produce the same expression profile will provide interventions that increase life span. In a further aspect, it has been discovered that test animals on a calorie restricted diet for a relatively short time have a similar gene expression profile to test animals which have been on a long term calorie restricted diet.

---------- KWIC ---------

Detail Description Table CWU - DETL (12):

10TABLE 10 mR: VAs decreased by age and returned to control levels by LT-CR GenBank Phenotype Immune System M30903 B lymphocyte kinase (Blk); **src**-family protein tyrosine kinase; plays important role in B-cell development/**activation** and immune responses; B-lineage cells U43384 Cytochrome

b-245, beta polypeptide (Cybb, cytochrome b558); integral component of the microbicidal oxidase electron transport chain of phagocytic cells, respiratory burst oxidase; phagocytes U10871 Mitogen **activated** protein kinase 14 (Mapk14); signal transduction, stimulate phosphorylation of transcription factors; major **upstream activator** of MAPKAP kinas 2; hematopoietic stem cells 222649 Myeloproliferative leukemia virus oncogene (Mpl); Member of hematopoietic cytokine receptor family, cell cycle regulator, induces proliferation and differentiation of hematopoietic cell lines; hematopoietic precursor cells, platelets and megakaryocytes Y07521 Potassium voltage gated channel, Shaw-related subfamily member 1 (Kcncl) potassium channels with properties of delayed rectifiers; nervous system, skeletal system, T lymphocytes U87456 Flavin-containing monooxygenase 1 (Fmol); xenobiotic metabolism; highly expressed in liver, lung, kidney, lower expressed in heart, spleen, testis, brain U40189 Pancreatic polypeptide receptor 1 (Ppyrl), neuropeptide Y receptor, peptide Y receptor; G-protein-coupled receptor; liver, gastrointestinal tract, prostate, neurons endocrine cells Neuron Specific U16297 Cytochrome b-561 (Cyb561); electron transfer protein unique to neuroendocrin secretory vesicles; vectoral transmembrane electron transport; brain D50032 Trans-golgi network protein 2 (Ttgn2); integral membrane protein localized to the trans-Golgi network; involved in the budding of exocytic transport vesicles; brain neurons Liver Specific/Ubiquitous D82019 Basigin (Bsg), CD147, neurothelin; membrane glycoprotein, immunoglobulin superfamily, homology to MHCs, acts as an adhesion molecule or a receptor, near: network formation and tumor progression; embryo, liver and other organs L38990 Glucokinase (Gk), key glycolytic enzyme; liver U50631 Heat-responsive protein 12 (Hrsp 12); heat-responsive, phosphorylated protein sequence simularity to Hsp70; liver, kidney U39818 Tuberous sclerosis 2 (Tsc2); mutationally inactivated in some families with tuberoi sclerosis; encodes a large, membrane-associated GTPase **activating** protein (GA tuberlin); may have a key role in the regulation of cellular growth; ubiquitous

PGPUB-DOCUMENT-NUMBER: 20030119732

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030119732 A1

TITLE: CDDO-compounds and combination therapies thereof

PUBLICATION-DATE: June 26, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Konopleva, Marina	Houston	TX	US	
Andreeff, Michael	Houston	TX	US	
Sporn, Michael B.	Tunbridge	VT	US	

APPL-NO: 09/ 998009

DATE FILED: November 28, 2001

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60253673 20001128 US

US-CL-CURRENT: 514/12

ABSTRACT:

CDDO-compounds in combination with other chemotherapeutic agents induce and potentiate cytotoxicity and apoptosis in cancer cell. One class of chemotherapeutic agents include retinoids. Cancer therapies based on these combination therapies are provided. Also provided are methods to treat graft versus host diseases using the CDDO compounds.

---------- KWIC ---------

Detail Description Table CWU - DETL (2):

2TABLE 1 Gene Source Human Disease Function Growth Factors FGF family member HST/KS Transfection INT-2 MMTV promoter FGF family member Insertion INTI/WNTI MMTV promoter Factor-like Insertion SIS Simian sarcoma virus PDGF B Receptor Tyrosine Kinases ERBB/HER Avian erythroblastosis Amplified, deleted EGF/TGF-.alpha./ virus; ALV promoter squamous cell Amphiregulin/ insertion; amplified cancer; glioblastoma Hetacellulin receptor human tumors ERBB-2/NEU/HER-2 Transfected from rat Amplified breast, Regulated by NDF/ Glioblastomas ovarian, gastric cancers Heregulin and EGF- Related factors FMS SM feline sarcoma virus CSF-1 receptor KIT HZ feline sarcoma virus MGF/Steel receptor Hematopoicis TRK Transfection from NGF (nerve growth human colon cancer Factor) receptor MET Transfection from Scatter factor/HGF human osteosarcoma Receptor RET Translocations and point Sporadic thyroid cancer;

Orphan receptor Tyr mutations familial medullary Kinase thyroid cancer; multiple endocrine neoplasias 2A and 2B ROS URII avian sarcoma Orphan receptor Tyr Virus Kinase PDGF receptor Translocation Chronic TEL(ETS-like Myelomonocytic transcription factor)/ Leukemia PDGF receptor gene Fusion TGF-.beta.receptor Colon carcinoma mismatch mutation target NONRECEPTOR TYROSINE KINASES ABI. Abelson Mul. V Chronic myelogenous Interact with RB, RNA leukemia translocation polymerase, CRK, with BCR CBL FPS/FES Avian Fujinami SV;GA FeSV LCK Mul.V (murine leukemia **Src** family; T cell virus) promoter signaling; interacts insertion CD4/CD8 T cells **SRC** Avian Rous sarcoma Membrane-associated Virus Tyr kinase with signaling function; **activated** by receptor kinases YES Avian Y73 virus **Src** family; signaling SER/THR PROTEIN KINASES AKT AKT8 murine retrovirus Regulated by PI(3)K?; regulate 70-kd S6 k? MOS Maloney murine SV GVBD; cystostatic factor; MAP kinase kinase PIM-1 Promoter insertion Mouse RAF/MIL 3611 murine SV; MH2 Signaling in RAS avian SV Pathway MISCELLANEOUS CELL SURFACE.sup.1 APC Tumor suppressor Colon cancer Interacts with catenins DCC Tumor suppressor Colon cancer CAM domains E-cadherin Candidate tumor Breast cancer Extracellular homotypic Suppressor binding; intracellular interacts with catenins PTC/NBCCS Tumor suppressor and Nevoid basal cell cancer 12 transmembrane Drosophilia homology syndrome (Gorline domain; signals syndrome) through Gli homogue Cl to antagonize hedgehog pathway TAN-1 Notch Translocation T-ALI. Signaling? homologue MISCELLANEOUS SIGNALING BCL-2 Translocation B-cell lymphoma Apoptosis CBL Mu Cas NS-1 V Tyrosine- Phosphorylated RING finger interact Abl CRK CT1010 ASV Adapted SH2/SH3 interact Abl DPC4 Tumor suppressor Pancreatic cancer TGF-.beta.-related signaling Pathway MAS Transfection and Possible angiotensin Tumorigenicity Receptor NCK Adaptor SH2/SH3 GUANINE NUCLEOTIDE EXCHANGERS AND BINDING PROTEINS BCR Translocated
with ABL Exchanger; protein in CML Kinase DBL Transfection Exchanger GSP NF-1 Hereditary tumor Tumor suppressor RAS GAP Suppressor neurofibromatosis OST Transfection Exchanger Harvey-Kirsten, N-RAS HaRat SV; Ki RaSV; Point mutations in many Signal cascade Balb-MoMuSV; human tumors Transfection VAV Transfection S112/S113; exchanger NUCLEAR PROTEINS AND TRANSCRIPTION FACTORS
BRCA1 Heritable suppressor Mammary Localization unsettled cancer/ovarian cancer BRCA2 Heritable suppressor Mammary cancer Function unknown ERBA Avian erythroblastosis thyroid hormone Virus receptor (transcription) ETS Avian E26 virus DNA binding EVII MuLV promotor AML Transcription factor Insertion FOS FBI/FBR murine 1 transcription factor osteosarcoma viruses with c-JUN GLI Amplified glioma Glioma Zinc finger; cubitus interruptus homologue is in hedgehog signaling pathway; inhibitory link PTC and hedgehog HMGI/LIM Translocation t(3:12) Lipoma Gene fusions high t(12:15) mobility group HMGI-C (XT-hook) and transcription factor LIM or acidic domain JUN ASV-17 Transcription factor AP-1 with FOS MLL/VHRK+ELI/MEN Translocation/fusion Acute myeloid leukemia Gene fusion of DNA- ELL with MLL binding and methyl Trithorax-like gene transferase MLL with ELI RNA pol II elongation factor MYB Avian myeloblastosis DNA binding Virus MYC Avian MC29; Burkitt's lymphoma DNA binding with Translocation B-cell MAX partner; cyclin Lymphomas; promoter regulation; interact Insertion avian RB?; regulate leukosis apoptosis? Virus N-MYC Amplified Neuroblastoma L-MYC Lung cancer REL Avian NF-.kappa.B family Retriculoendotheliosis transcription factor Virus SKI Avian SKV770 Transcription factor Retrovirus VHL Heritable suppressor Von Hippel-Landau Negative regulator or syndrome elongin;

transcriptional elongation complex WT-1 Wilm's tumor Transcription factor CELL CYCLE/DNA DAMAGE RESPONSE.sup.10-21 ATM Hereditary disorder Ataxia-telangiectasia Protein/lipid kinase homology; DNA damage response **upstream** in P53 pathway BCL-2 Translocation Follicular lymphoma Apoptosis FACC Point mutation Fanconi's anemia group C (predisposition leukemia MDA-7 Fragile site 3p14.2 Lung carcinoma Histidine triad-related diadenosine 5',3""- tetraphosphate asymmetric hydrolase hMLI/MutL HNPCC Mismatch repair; MutL Homologue hMSH2/MutS HNPCC Mismatch repair; MutS Homologue hPMS1 HNPCC Mismatch repair; MutL Homologue hPMS2 HNPCC Mismatch repair; MutL Homologue INK4/MTS1 Adjacent INK-4B at Candidate MTS1 p16 CDK inhibitor 9p21; CDK complexes suppressor and MLM melanoma gene INK4B/MTS2 Candidate suppressor p15 CDK inhibitor MDM-2 Amplified Sarcoma Negative regulator p53 p53 Association with SV40 Mutated > 50% human Transcription factor; T antigen tumors, including checkpoint control; hereditary Li-Fraumeni apoptosis syndrome PRAD1/BCL1 Translocation with Parathyroid adenoma; Cyclin D Parathyroid hormone B-CLL or IgG RB Hereditary Retinoblastoma; Interact cyclin/cdk; Retinoblastoma; osteosarcoma; breast regulate E2F Association with many cancer; other sporadic transcription factor DNA virus tumor cancers Antigens XPA xerodema Excision repair; photo- pigmentosum; skin product recognition; cancer predisposition zinc finger

PGPUB-DOCUMENT-NUMBER: 20030119067

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030119067 A1

TITLE: PYK2 related products and methods

PUBLICATION-DATE: June 26, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Lev, Sima	San Carlos	CA	US	
Schlessinger, Joseph	Woodbridge	CT	US	

APPL-NO: 10/ 292524

DATE FILED: November 13, 2002

RELATED-US-APPL-DATA:

child 10292524 A1 20021113

parent continuation-of 08987689 19971209 US ABANDONED

non-provisional-of-provisional 60032824 19961211 US

US-CL-CURRENT: 435/7.1, 435/194 , 435/320.1 , 435/325 , 435/69.1 , 514/249 , 514/266.1 , 514/311 , 514/376

ABSTRACT:

The present invention features a method for treatment of an organism having a disease or condition characterized by an abnormality in a signal transduction pathway, wherein the signal transduction pathway includes a PYK2 protein. The invention also features methods for diagnosing such diseases and for screening for agents that will be useful in treating such diseases. The invention also features purified and/or isolated nucleic acid encoding a PYK2 protein.

RELATED APPLICATIONS

[0001] The present application is related to U.S. Serial No. 60/032,824, filed Dec. 11, 1996, entitled to PYK2 RELATED PRODUCTS AND METHODS, by Lev et al. (Lyon & Lyon Docket No. 222/126). This application is also related to U.S. application Ser. No. 08/460,626, filed Jun. 2, 1995, which is a continuation-in-part application of U.S. patent application Ser. No. 08/357,642, filed Dec. 15, 1994, both of which are incorporated herein by reference in their entirety, including any drawings.

--------- KWIC ---------

Detail Description Paragraph - DETX (16):

[0078] We further analyzed agonist-induced MAP kinase activity in PC12 cell lines which stably overexpress a dominant interfering mutant of Grb2 lacking the N-terminal SH3 domain (Grb2 DN-SH3) or in PC12 cells which stably overexpress the proline rich tail of Sos (Sos-CT). Xie et al., J. Biol. Chem. 270, 30717-30724 (1995); Gishizky et al., Proc. Natl. Acad. Sci. USA 92, 10889-10893 (1995). Overexpression of Grb2 DN-SH3 in PC12 cells completely blocked LPA- or bradykinin-induced MAP kinase **activation**. Overexpression of Sos-CT strongly reduced MAP kinase **activation** in response to LPA and bradykinin stimulation. However, **activation** of PYK2 or **Src** was not affected by the dominant interfering mutants of Grb2 and Sos confirming that PYK2 and **Src** act **upstream** of Grb2 and Sos in the cascade of events leading to MAP kinase **activation**.

PGPUB-DOCUMENT-NUMBER: 20030113897

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030113897 A1

TITLE: Mutant p21Cip1/WAF1 and cell growth control and cell growth control

PUBLICATION-DATE: June 19, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Hung, Mien-Chie	Houston	TX	US	
Zhou, Binhua P.	Houston	TX	US	

APPL-NO: 10/ 142174

DATE FILED: May 9, 2002

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60289651 20010509 US

US-CL-CURRENT: 435/226, 435/320.1 , 435/325 , 435/69.1 , 536/23.2

ABSTRACT:

Disclosed are methods and compositions regarding separate mutant forms of p21.sup.Cip1/WAF1 that are associated with control of cell growth. Substitution of Thr.sup.145 with another amino acid, such as Ala, results in failure to be phosphorylated at that site and leads to retention of the polypeptide in the nucleus, resulting in preferentially suppressing growth of transformed cells. Alternatively, substitution of Thr.sup.145 with another amino acid, such as Asp, results in cytoplasmic translocation of the polypeptide and results in enhancing cellular survival.

[0001] This application claims priority to U.S. Provisional Patent Application Serial No. 60/289,651, filed May 9, 2001, incorporated by reference herein in its entirety.

---------- KWIC ---------

Detail Description Table CWU - DETL (3):

3TABLE 2 Oncogenes Gene Source Human Disease Function Growth Factors.sup.1 HST/KS Transfection FGF family member INT-2 MMTV promoter FGF family member Insertion INTI/WNTI MMTV promoter Factor-like Insertion SIS Simian sarcoma PDGF B virus Receptor Tyrosine Kinases.sup.1, 2 ERBB/HER Avian Amplified, deleted EGF/TGF-.alpha./ erythroblastosis squamous cell

amphiregulin/ virus; ALV cancer; hetacellulin promoter glioblastoma receptor insertion; amplified human tumors ERBB-2/NEU/HER-2 Transfected from rat Amplified breast, Regulated by NDF/ Glioblatoms ovarian, gastric heregulin and cancers EGF- related factors FMS SM feline sarcoma CSF-1 receptor virus KIT HZ feline sarcoma MGF/Steel receptor virus hematopoieis TRK Transfection from NGF (nerve growth human colon factor) receptor cancer MET Transfection from Scatter factor/HGF human receptor osteosarcoma RET Translocations and Sporadic thyroid Orphan receptor Tyr point mutations cancer; kinase familial medullary thyroid cancer; multiple endocrine neoplasias 2A and 2B ROS URII avian sarcoma Orphan receptor Tyr Virus kinase PDGF receptor Translocation Chronic TEL(ETS-like myclomonocytic transcription leukemia factor)/ PDGF receptor gene fusion TGF-.beta. receptor Colon carcinoma mismatch mutation target NONRECEPTOR TYROSINE KINASES.sup.1 ABI. Abelson Mul. V Chronic Interact with RB, myelogenous RNA leukemia polymerase, CRK, translocation CBL with BCR FPS/FES Avian Fujinami SV; GA FeSV LCK Mul. V (murine **Src** family; T cell leukemia signaling; interacts virus) promoter CD4/CD8 T cells insertion **SRC** Avian Rous Membrane- sarcoma associated Tyr Virus kinase with signaling function; **activated** by receptor kinases YES Avian Y73 virus **Src** family; signaling SER/THR PROTEIN KINASES.sup.1 AKT AKT8 murine Regulated by retrovirus PI(3)K?; regulate 70-kd S6 k? MOS Maloney murine SV GVBD; cystostatic factor; MAP kinase kinase PIM-1 Promoter insertion Mouse RAF/MIL 3611 murine SV; Signaling in RAS MH2 pathway avian SV MISCELLANEOUS CELL SURFACE.sup.1 APC Tumor suppressor Colon cancer Interacts with catenins DCC Tumor suppressor Colon cancer CAM domains E-cadherin Candidate tumor Breast cancer Extracellular Suppressor homotypic binding; intracellular interacts with catenins PTC/NBCCS Tumor suppressor Nevoid basal cell 12 transmembrane and cancer domain; signals Drosophilia syndrome (Gorline through Gli homology syndrome) homogue CI to antagonize hedgehog pathway TAN-1 Notch Translocation T-ALI. Signaling? homologue MISCELLANEOUS SIGNALING.sup.1, 3 BCL-2 Translocation B-cell lymphoma Apoptosis CBL Mu Cas NS-1 V Tyrosine- phosphorylated RING finger interact Abl CRK CT1010 ASV Adapted SH2/SH3 interact Abl DPC4 Tumor suppressor Pancreatic cancer TGF-.beta.-related signaling pathway MAS Transfection and Possible angiotensin Tumorigenicity receptor NCK Adaptor SH2/SH3 GUANINE NUCLEOTIDE EXCHANGERS AND BINDING PROTEINS.sup.3, 4 BCR Translocated with Exchanger; protein ABL in CML kinase DBL Transfection Exchanger GSP NF-1 Hereditary tumor Tumor suppressor RAS GAP Suppressor neurofibromatosis OST Transfection Exchanger Harvey-Kirsten, N- HaRat SV; Ki Point mutations in Signal cascade RAS RaSV; many Balb-MoMuSV; human tumors Transfection VAV Transfection S112/S113; exchanger NUCLEAR PROTEINS AND TRANSCRIPTION FACTORS.sup.1, 5-9 BRCA1 Heritable suppressor Mammary Localization cancer/ovarian unsettled cancer BRCA2 Heritable suppressor Mammary cancer Function unknown ERBA Avian thyroid hormone erythroblastosis receptor Virus (transcription) ETS Avian E26 virus DNA binding EVII MuLV promoter AML Transcription factor Insertion FOS FBI/FBR murine 1 transcription osteosarcoma factor viruses with c-JUN GLI Amplified glioma Glioma Zinc finger; cubitus interruptus homologue is in hedgehog signaling pathway; inhibitory link PTC and hedgehog HMGG/LIM Translocation Lipoma Gene fusions high t(3:12) mobility group t(12:15) HMGI-C (XT- hook) and transcription factor LIM or acidic domain JUN ASV-17 Transcription factor AP-1 with FOS MLL/VHRX + Translocation/fusion Acute myeloid Gene fusion of ELI/MEN ELL with MLL leukemia DNA- Trithorax-like gene binding and methyl transferase MLL with ELI RNA pol II elongation factor MYB Avian DNA binding myeloblastosis .

Virus MYC Avian MC29; Burkitt's lymphoma DNA binding with Translocation B-MAX partner; cell cyclin Lymphomas; regulation; interact promoter RB?; regulate Insertion avian apoptosis? leukosis Virus N-MYC Amplified Neuroblastoma L-MYC Lung cancer REL Avian NF-.kappa.B family Retriculoendotheliosis transcription factor Virus SKI Avian SKV770 Transcription factor Retrovirus VHL Heritable suppressor Von Hippel-Landau Negative regulator syndrome or elongin; transcriptional elongation complex WT-1 Wilm's tumor Transcription factor CELL CYCLE/DNA DAMAGE RESPONSE.sup.10-21 ATM Hereditary disorder Ataxia- Protein/lipid kinase telangiectasia homology; DNA damage response **upstream** in P53 pathway BCL-2 Translocation Follicular Apoptosis lymphoma FACC Point mutation Fanconi's anemia group C (predisposition leukemia FHIT Fragile site 3p14.2 Lung carcinoma

PGPUB-DOCUMENT-NUMBER: 20030091539

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030091539 A1

TITLE: Use of DF3/MUC1 regulated expression in gene therapy

PUBLICATION-DATE: May 15, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Weichselbaum, Ralph R.	Chicago	IL	US	
Kufe, Donald W.	Wellesley	MA	US	

APPL-NO: 10/ 244705

DATE FILED: September 16, 2002

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60322265 20010914 US

US-CL-CURRENT: 424/93.2, 435/235.1 , 435/320.1 , 435/456 , 514/44

ABSTRACT:

The present invention provides for improved vectors for use in gene therapy. Utilizing the cancer specific DF3/MUC1 promoter to drive a replication essential gene, vectors are made conditionally replication-competent, permitting wider infection and expression of tumor cells. In addition, therapeutic genes and adjunct therapies further increase anti-tumor efficacy.

[0001] The present patent application claims priority to U.S. Provisional Patent Application Serial No. 60/322,265, filed Sep. 14, 2001. The entire text of the above-referenced disclosure is specifically incorporated by reference herein without disclaimer.

---------- KWIC ---------

Detail Description Table CWU - DETL (2):

2TABLE 2 Oncogenes Gene Source Human Disease Function Growth Factors FGF family member HST/KS Transfection INT-2 MMTV promoter FGF family member Insertion INTI/WNTI MMTV promoter Factor-like Insertion SIS Simian sarcoma virus PDGF B Receptor Tyrosine Kinases ERBB/HER Avian erythroblastosis Amplified, deleted EGF/TGF-/ virus; ALV promoter Squamous cell Amphiregulin/ insertion; amplified Cancer; glioblastoma Hetacellulin receptor human tumors ERBB-2/NEU/HER-2 Transfected from rat Amplified breast, Regulated by NDF/ Glioblastomas Ovarian, gastric cancers Heregulin and EGF- Related factors FMS

SM feline sarcoma virus CSF-1 receptor KIT HZ feline sarcoma virus MGF/Steel receptor Hematopoieis TRK Transfection from NGF (nerve growth human colon cancer Factor) receptor MET Transfection from Scatter factor/HGF human osteosarcoma Receptor RET Translocations and point Sporadic thyroid cancer; Orphan receptor Tyr mutations Familial medullary Kinase Thyroid cancer; Multiple endocrine Neoplasias 2A and 2B ROS URII avian sarcoma Orphan receptor Tyr Virus Kinase PDGF receptor Translocation Chronic TEL(ETS-like Myelomonocytic transcription factor)/ Leukemia PDGF receptor gene Fusion TGF-receptor Colon carcinoma Mismatch mutation Target NONRECEPTOR TYROSINE KINASES ABI. Abelson Mul.V Chronic myelogenous Interact with RB, RNA Leukemia translocation polymerase, CRK, With BCR CBL FPS/FES Avian Fujinami SV;GA FeSV LCK Mul.V (murine leukemia **Src** family; T cell virus) promoter signaling; interacts insertion CD4/CD8 T cells **SRC** Avian Rous sarcoma Membrane-associated Tyr Virus kinase with signaling function; **activated** by , receptor kinases YES Avian Y73 virus **Src** family; signaling SER/THR PROTEIN KINASES AKT AKT8 murine retrovirus Regulated by PI(3)K?; regulate 70-kd S6 k? MOS Maloney murine SV GVBD; cystostatic factor; MAP kinase kinase PIM-1 Promoter insertion Mouse RAF/MIL 3611 murine SV; MH2 Signaling in RAS avian SV Pathway MISCELLANEOUS CELL SURFACE.sup.1 APC Tumor suppressor Colon cancer Interacts with catenins DCC Tumor suppressor Colon cancer CAM domains E-cadherin Candidate tumor Breast cancer Extracellular homotypic Suppressor binding; intracellular interacts with catenins PTC/NBCCS Tumor suppressor and Nevoid basal cell cancer 12 transmembrane Drosophilia homology Syndrome (Gorline domain; signals Syndrome) through Gli homogue Cl to antagonize hedgehog pathway TAN-1 Notch homologue Translocation T-ALI. Signaling? MISCELLANEOUS SIGNALING BCL-2 Translocation B-cell lymphoma Apoptosis CBL Mu Cas NS-1 V Tyrosine- Phosphorylated RING finger interact Abl CRK CT1010 ASV Adapted SH2/SH3 interact Abl DPC4 Tumor suppressor Pancreatic cancer TGF-related signaling Pathway MAS Transfection and Possible angiotensin Tumorigenicity Receptor NCK Adaptor SH2/SH3 GUANINE NUCLEOTIDE EXCHANGERS AND BINDING PROTEINS BCR Translocated with ABL Exchanger; protein In CML Kinase DBL Transfection Exchanger GSP NF-1 Hereditary tumor Tumor suppressor RAS GAP Suppressor Neurofibromatosis OST Transfection Exchanger Harvey-Kirsten, N-RAS HaRat SV; Ki RaSV; Point mutations in many Signal cascade Balb-MoMuSV; Human tumors Transfection VAV Transfection S112/S113; exchanger NUCLEAR PROTEINS AND TRANSCRIPTION FACTORS BRCA1 Heritable suppressor Mammary Localization unsettled cancer/ovarian cancer BRCA2 Heritable suppressor Mammary cancer Function unknown ERBA Avian erythroblastosis thyroid hormone Virus receptor (transcription) ETS Avian E26 virus DNA binding EVII MuL V promotor AML Transcription factor Insertion FOS FBI/FBR murine 1 transcription factor osteosarcoma viruses with c-JUN GLI Amplified glioma Glioma Zinc finger; cubitus interruptus homologue is in hedgehog signaling pathway; inhibitory link PTC and hedgehog HMGI/LIM Translocation t(3:12) Lipoma Gene fusions high t(12:15) mobility group HMGI-C (XT-hook) and transcription factor LIM or acidic domain JUN ASV-17 Transcription factor AP-1 with FOS MLL/VHRX + ELI/MEN Translocation/fusion Acute myeloid Gene fusion of DNA- ELL with MLL leukemia binding and methyl Trithorax-like gene transferase MLL with ELI RNA pol II elongation factor MYB Avian myeloblastosis DNA binding Virus MYC Avian MC29; Burkitt's lymphoma DNA binding with Translocation B-cell MAX partner; cyclin Lymphomas; promoter regulation; interact Insertion avian leukosis RB?; regulate Virus apoptosis? N-MYC Amplified Neuroblastoma L-MYC Lung cancer REL Avian NF-B family Retriculoendotheliosis transcription factor Virus SK1

Avian SKV770 Transcription factor Retrovirus VHL Heritable suppressor Von Hippel-Landau Negative regulator or Syndrome elongin; transcriptional elongation complex WT-1 Wilm's tumor Transcription factor CELL CYCLE/DNA DAMAGE RESPONSE ATM Hereditary disorder Ataxia-telangiectasia Protein/lipid kinase homology; DNA damage response **upstream** in P53 pathway BCL-2 Translocation Follicular lymphoma Apoptosis FACC Point mutation Fanconi's anemia group C (predisposition Leukemia MDA-7 Fragile site 3p14.2 Lung carcinoma Histidine triad-related diadenosine 5,3- tetraphosphate asymmetric hydrolase hMLI/MutL HNPCC Mismatch repair; MutL Homologue hMSH2/MutS HNPCC Mismatch repair; MutS Homologue hPMS1 HNPCC Mismatch repair; MutL Homologue hPMS2 HNPCC Mismatch repair; MutL Homologue INK4/MTS1 Adjacent INK-4B at Candidate MTS1 p16 CDK inhibitor 9p21; CDK complexes Suppressor and MLM melanoma gene INK4B/MTS2 Candidate suppressor p15 CDK inhibitor MDM-2 Amplified Sarcoma Negative regulator p53 P53 Association with SV40 Mutated >50% human Transcription factor; T antigen tumors, including checkpoint control; hereditary Li- apoptosis Fraumeni syndrome PRAD1/BCL1 Translocation with Parathyroid adenoma; Cyclin D Parathyroid hormone B-CLL or IgG RB Hereditary Retinoblastoma; Interact cyclin/cdk; Retinoblastoma; Osteosarcoma; breast regulate E2F Association with many cancer; other transcription factor DNA virus tumor sporadic Antigens cancers XPA Xeroderma Excision repair; photo- pigmentosum; skin product recognition; cancer predisposition

PGPUB-DOCUMENT-NUMBER: 20030083231

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030083231 A1

TITLE: Blood cell deficiency treatment method

PUBLICATION-DATE: May 1, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Ahlem, Clarence N.	San Diego	CA	US	
Reading, Christopher	San Diego	CA	US	
Frincke, James	San Diego	CA	US	
Stickney, Dwight	Granite Bay	CA	US	
Lardy, Henry A.	Madison	WI	US	
Marwah, Padma	Middleton	WI	US	
Marwah, Ashok	Middleton	WI	US	
Prendergast, Patrick T.	Straffan		IE	

APPL-NO: 10/ 087929

DATE FILED: March 1, 2002

RELATED-US-APPL-DATA:

child 10087929 A1 20020301

parent continuation-in-part-of 09675470 20000928 US PENDING

child 10087929 A1 20020301

parent continuation-in-part-of 09820483 20010329 US PENDING

child 09820483 20010329 US

parent continuation-in-part-of 09535675 20000323 US PENDING

child 09820483 20010329 US

parent continuation-in-part-of 09449004 19991124 US ABANDONED

child 09820483 20010329 US

parent continuation-in-part-of 09449184 19991124 US ABANDONED

child 09820483 20010329 US

parent continuation-in-part-of 09449042 19991124 US ABANDONED

child 09820483 20010329 US

parent continuation-in-part-of 09461026 19991215 US ABANDONED

child 09820483 20010329 US

parent continuation-in-part-of 09586673 20000601 US ABANDONED

child 09820483 20010329 US

parent continuation-in-part-of 09586672 20000601 US ABANDONED

child 09820483 20010329 US

parent continuation-in-part-of 09414905 19991008 US ABANDONED

non-provisional-of-provisional 60161453 19991025 US

non-provisional-of-provisional 60272624 20010301 US

non-provisional-of-provisional 60323016 20010911 US

non-provisional-of-provisional 60340045 20011130 US

non-provisional-of-provisional 60328738 20011011 US

non-provisional-of-provisional 60338015 20011108 US

non-provisional-of-provisional 60343523 20011220 US

non-provisional-of-provisional 60126056 19991019 US

non-provisional-of-provisional 60124087 19990311 US

non-provisional-of-provisional 60109923 19981124 US

non-provisional-of-provisional 60109924 19981124 US

non-provisional-of-provisional 60110127 19981127 US

non-provisional-of-provisional 60112206 19981215 US

non-provisional-of-provisional 60145823 19990727 US

non-provisional-of-provisional 60137745 19990603 US

non-provisional-of-provisional 60140028 19990616 US

US-CL-CURRENT: 514/2, 514/169 , 514/173 , 514/26 , 514/44 , 514/63

ABSTRACT:

The invention relates to the use of compounds to treat a number of conditions,

such as thrombocytopenia, neutropenia or the delayed effects of radiation therapy. Compounds that can be used in the invention include methyl-2,3,4-trihydroxy-1-O-(7,17-dioxoandrost-5-ene-3.beta.-yl)-.beta.-D--glucopyranosiduronate, 16.alpha.,3.alpha.-dihydroxy-5.alpha.-androstan-17--one or 3,7,16,17-tetrahydroxyandrost-5-ene, 3,7,16,17-tetrahydroxyandrost--4-ene,3,7,16,17-tetrahydroxyandrost-1-ene or 3,7,16,17-tetrahydroxyandrostane that can be used in the treatment method.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of: (1) pending U.S. application Ser. No. 09/675,470, filed Sep. 28, 2000, which is a continuation-in-part of abandoned U.S. provisional application Ser. No. 60/161,453, filed Oct. 25, 1999, and (2) pending U.S. provisional application Ser. No. 60/272,624, filed Mar. 1, 2001, and (3) pending U.S. provisional application Ser. No. 60/323,016, filed Sep. 10, 2001, and (4) pending U.S. provisional application Ser. No. 60/340,045, filed Nov. 1, 2001, and (5) pending U.S. provisional application Ser. No. 60/328,738, filed Oct. 11, 2001, and (6) pending U.S. provisional application Ser. No. 60/338,015, filed Nov. 8, 2001, and (7) pending U.S. provisional application Ser. No. 60/343,523, filed Dec. 20, 2001, and (8) pending U.S. application Ser. No. 09/820,483, filed Mar. 29, 2001, which is a continuation-in-part of pending U.S. application Ser. No. 09/535,675, filed Mar. 23, 2000, which is a continuation-in-part of abandoned U.S. provisional application Ser. No. 60/126,056, filed Mar. 23, 1999, and abandoned U.S. provisional application Ser. No. 60/124,087, filed Mar. 11, 1999 and which is a continuation-in-part of abandoned U.S. application Ser. No. 09/449,004, filed Nov. 24, 1999, which is a continuation-in-part of abandoned U.S. provisional application Ser. No. 60/109,923, filed Nov. 24, 1998, and which is a continuation-in-part of abandoned U.S. application Ser. No. 09/449,184, filed Nov. 24, 1999, which is a continuation-in-part of abandoned U.S. provisional application Ser. No. 60/109,924, filed Nov. 24, 1998, and which is a continuation-in-part of abandoned U.S. application Ser. No. 09/449,042, filed Nov. 24, 1999, which is a continuation-in-part of abandoned U.S. provisional application Ser. No. 60/110,127, filed Nov. 27, 1998, and which is a continuation-in-part of pending U.S. application Ser. No. 09/461,026, filed Dec. 15, 1999, which is a continuation-in-part of abandoned U.S. provisional application Ser. No. 60/112,206, filed Dec. 15, 1998, and which is a continuation-in-part of abandoned U.S. application Ser. No. 09/586,673, filed Jun. 1, 2000, which is a continuation-in-part of abandoned U.S. provisional application Ser. No. 60/145,823, filed Jul. 27, 1999, and which is a continuation-in-part of abandoned U.S. application Ser. No. 09/586,672, filed Jun. 1, 2000, which is a continuation-in-part of abandoned U.S. provisional application Ser. No. 60/137,745, filed Jun. 3, 1999, and which is a continuation-in-part of abandoned U.S. application Ser. No. 09/414,905, filed Oct. 8, 1999, which is a continuation-in-part of abandoned U.S. provisional application Ser. No. 60/140,028, filed Jun. 16, 1999, all of which are incorporated herein by reference in their entireties.

---------- KWIC ---------

Summary of Invention Paragraph - BSTX (858):

[0856] Additional exemplary mammalian or human and other biomolecules, e.g., transcription factors or receptors, including orphan nuclear receptors, their homologs, isoforms and co-factors (e.g., co-repressors, co-**activators,** transcription factors, gene promoter regions or sequences) and related molecules that the formula 1 compounds can directly or indirectly from complexes with, or modulate (detectably increase or decrease) the synthesis, level or one or more biological activities of, include steroidogenic factor-1 (SF-1), steroidogenic acute regulatory protein (StAR), chicken ovalbumin **upstream** promoter-transcription factor (COUP-TFI) and its mammalian homologs, silencing mediator for retinoid and thyroid hormone receptor (SMRT) and its mammalian homologs, sterol regulatory element binding protein (SREBP) 1a (SREBP-1a), SREBP-1c, SREPB-2, NF-E3, FKHR-Li, COUP-TFII and its mammalian homologs, I.kappa.B, I.kappa.B.alpha., AML-3, PEBP2.alpha.A1, Osf2, Cbfa1, RUNX2, **activating** transcription factor 2 (ATF2), c-Jun, c-Fos, a mitogen **activated** kinase (MAP) such as p38 or JNK or an isoform thereof, a mitogen **activated** kinase kinase (MKK) or an isoform thereof, steroid receptor coactivator-1 family (**SRC**-1, **SRC**-1/serum response factor), **SRC**-2, **SRC**-3, SET, nerve growth factor inducible protein B, StF-IT, NFAT, NFAT interacting protein 45 (NIP45), IkB, an IkB kinase, NFATp, NFAT4, an AP-1 family protein, p300, CREB, CREB-binding protein (CPB), p300/CBP, p300/CPB-associated factor, SWI/SNF and their human and other homologs, BRG-1, OCT-1/OAF, AP-1, AF-2, Ets, androgen receptor associated protein 54 (ARA54), androgen receptor associated protein 55 (ARA55), androgen receptor associated protein 70 (ARA70), androgen receptor-interacting protein 3 (ARIP3), ARIP3/PIASx .alpha. complex, PIASx .alpha., Miz1, Miz1/PIASx .beta. complex, PIASx .beta., PIAS1, PIAS3, GBP, GBP/PIAS1 complex, RAC3/ACTR complex, **SRC**-1.alpha., receptor interacting protein-140 (RIP-140), transcription factor **activator** protein-1, **activation** function-2, glucocorticoid receptor-interacting protein-1 (GRIP-1), receptor interacting protein-160 (RIP-160), suppressor of gal4D lesions (SUG-1), transcription intermediary factor-1 (TIF-1), transcription intermediary factor-2 (TIF-2), SMRT, N-CoR, N-CoA-1, p/CIP, p65 (RelA), the 120 KD rel-related transcription factor, heat shock proteins (HSP) such as HSP90, HSP70 and HSP72, heat shock factor-1, Vpr encoded by the human immunodeficiency virus and its isoforms and homologs thereof, testicular orphan receptor TR2, thyroid hormone .alpha.1 (TR .alpha.1), retinoid X receptor .alpha., TR .alpha.1/RXR .alpha. heterodimer, direct repeat-4 thyroid hormone response element (DR.sup.4-TRE), an estrogen receptor (ER) such as ER.alpha. or ER.beta., estrogen receptor related receptor .alpha. (ERR.alpha.), estrogen receptor related receptor .beta. (ERR.beta.), estrogen receptor related receptor .gamma. (ERR.gamma.), steroid xenobiotic receptor (SXR), hepatocyte nuclear factor 4 (HNF-4), hepatocyte nuclear factor 3 (HNF-3), liver X receptors (LXRs), LXR.alpha., LXR.beta., estrogen receptor .alpha. (ER.alpha.), constitutive androstane receptor-.beta. (CAR-.beta.), RXR/CAR-.beta. heterodimer, short heterodimer partner (SHP; NR0B2), SHP/ER.alpha. heterodimer, estrogen receptor .beta., SHP/ER.beta. heterodimer, testicular orphan receptor TR4, TR2/TR4 heterodimer, pregnane X receptor (PXR) and isoforms, cytochrome P-450 monooxygenase 3A4, including its gene promoter region and isoforms thereof, HNF-4/cytochrome P-450 monooxygenase 3A4 gene promoter region and isoforms complex, HIV-1 long terminal repeat (LTR), HIV-2 LTR, TR2/HIV-1 LTR complex, TR4/HIV-1 LTR complex, TR4/HIV-1 LTR complex, TR .alpha.1/TR4/HIV-1 LTR complex, TR2 isoforms (TR2-5, TR7, TR9, TR11), DAX-1, DAX-1/steroidogenic acute regulatory protein gene promoter

region, RevErb, Rev-erbA .alpha., Rev-erb .beta., steroid receptor coactivator amplified in breast cancer (AIB 1), p300/CREB binding protein-interacting protein (p/CIP), thyroid hormone receptor (TR, T3R), thyroid hormone response elements (T3REs), retinoblastoma protien (Rb), tumor suppressor factor p53, transcription factor E2F, mammalian acute phase response factor (APRF), constitutive androstane receptor (CAR), Xenopus xSRC-3 and mammalian (human) homologs, TAK1, TAK1/peroxisome proliferator-**activated** receptor .alpha. (PPAR.alpha.) complex, PPAR.alpha./RXR.alpha. complex, peroxisome proliferator-**activated** receptor .beta. (PPAR.beta.), peroxisome proliferator-**activated** receptor .gamma. (PPAR.gamma.), peroxisome proliferator-**activated** receptor .delta. (PPAR.delta.), farnesoid X receptor, retina X receptor, TAK-1/RIP-140 complex, retinoic acid receptor (RAR), RAR.beta., TR4/RXRE complex, SF-1/steroid hydroxylase gene promoter region, SF-1/oxytocin, including its gene promoter region, bile acid receptor (FXR), nuclear receptor corepressor (NcoR), liver receptor homologous protein-1 (LRH-1; NR5A2), SF-1/ACTH receptor gene promoter region, rat Ear-2 and mammalian homologs, human TR3 orphan receptor (TR3), RLD-1, OR-1, androgen receptor, glucocorticoid receptor, estrogen receptor, progesterone receptor, mineralcorticoid receptor, aldosterone receptor, E6-associated protein (E6-AP), OR1, OR1/RXR.alpha. complex, TIF-1, CBP/P300 complex, TRIP1/SUG-1 complex, RIP-140, steroid receptor coactivator 1 (SRC1), SRC1.alpha./P160 complex and TIF-2/GRIP-1 complex, RAR/N-CoR/RIP13 complex, RAR/SMRT/TRAC-2 complex and protein X of hepatitis B virus. The homologs, orthologs and isoforms of these transcription factors, receptors and other molecules are included among the molecules that the formula 1 compounds can modulate the synthesis or one or more biological activities of. Such factors are bioogically active or function in one or more of a number of cell types such as T cells, B cells, macrophages, dendritic cells, platelets, monocytes, neutrophils, neurons, epithelial cells, endothelial cells, cartilage cells, osteoblasts, osteoclasts, splenocytes, thymocytes and GALT associated cells. Methods to identify these molecules and their biological activities have been described, e.g., U.S. Pat. Nos. 6,248,781, 6,242,253, 6,180,681, 6,174,676, 6,090,561, 6,090,542, 6,074,850, 6,063,583, 6,051,373, 6,024,940, 5,989,810, 5,958,671, 5,925,657, 5,958,671, 5,844,082, 5,837,840, 5,770,581, 5,756,673, and PCT publication Nos. WO 00/24245, WO 0073453 and WO 97/39721.

PGPUB-DOCUMENT-NUMBER: 20030082722

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030082722 A1

TITLE: Method for amplifying expression from a cell specific promoter

PUBLICATION-DATE: May 1, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Fang, Bingliang	Pearland	TX	US	

APPL-NO: 10/ 212667

DATE FILED: August 5, 2002

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60310905 20010808 US

US-CL-CURRENT: 435/69.1, 435/320.1 , 435/325 , 435/455

ABSTRACT:

The present invention provides, in one aspect, methods for selective expressing gene products using a binary or bicistronic expression system based on the use of a tissue-preferential promoter to drive expression of a transcriptional activator, which in turn drives a gene of interest. In another aspect, the invention provides for methods of cancer therapy comprising expressing Bax, TRAIL or various other therapeutic proteins using a tissue preferential promoter such as hTERT or CEA, optionally coupled with a binary or a bicistronic expression system.

[0001] The present application claims priority to co-pending U.S. Provisional Patent Application Serial No. 60/310,905 filed on Aug. 8, 2001. The entire text of the above-referenced disclosure is specifically incorporated herein by reference without disclaimer.

---------- KWIC ---------

Detail Description Table CWU - DETL (1):

1TABLE 1 Oncogenes Gene Source Human Disease Function Growth Factors FGF family member HST/KS Transfection INT-2 MMTV promoter FGF family member Insertion INTI/WNTI MMTV promoter Factor-like Insertion SIS Simian sarcoma virus PDGF B Receptor Tyrosine Kinases ERBB/HER Avian erythroblastosis Amplified, deleted EGF/TGF-.alpha./ virus; ALV promoter squamous cell

amphiregulin/ insertion; amplified cancer; glioblastoma hetacellulin receptor human tumors ERBB-2/NEU/HER-2 Transfected from rat Amplified breast, Regulated by NDF/ Glioblatoms ovarian, gastric cancers heregulin and EGF- related factors FMS SM feline sarcoma virus CSF-1 receptor KIT HZ feline sarcoma virus MGF/Steel receptor hematopoieis TRK Transfection from NGF (nerve growth human colon cancer factor) receptor MET Transfection from Scatter factor/HGF human osteosarcoma receptor RET Translocations and point Sporadic thyroid cancer; Orphan receptor Tyr mutations familial medullary kinase thyroid cancer; multiple endocrine neoplasias 2A and 2B ROS URII avian sarcoma Orphan receptor Tyr Virus kinase PDGF receptor Translocation Chronic TEL(ETS-like myclomonocytic transcription factor)/ leukemia PDGF receptor gene fusion TGF-.beta. receptor Colon carcinoma mismatch mutation target NONRECEPTOR TYROSINE KINASES ABI. Abelson Mul. V Chronic myelogenous Interact with RB, RNA leukemia translocation polymerase, CRK, with BCR CBL FPS/FES Avian Fujinami SV;GA FeSV LCK Mul. V (murine leukemia **Src** family; T cell virus) promoter signaling; interacts insertion CD4/CD8 T cells **SRC** Avian Rous sarcoma Membrane-associated Virus Tyr kinase with signaling function; **activated** by receptor kinases YES Avian Y73 virus **Src** family; signaling SER/THR PROTEIN KINASES AKT AKT8 murine retrovirus Regulated by PI(3)K; regulate 70-kd S6 k MOS Maloney murine SV GVBD; cystostatic factor; MAP kinase kinase PIM-1 Promoter insertion Mouse RAF/MIL 3611 murine SV; MH2 Signaling in RAS avian sv pathway MISCELLANEOUS CELL SURFACE APC Tumor suppressor Colon cancer Interacts with catenins DCC Tumor suppressor Colon cancer CAM domains E-cadherin Candidate tumor Breast cancer Extracellular homotypic Suppressor binding; intracellular interacts with catenins PTC/NBCCS Tumor suppressor and Nevoid basal cell cancer 12 transmembrane Drosophilia homology syndrome (Gorline domain; signals syndrome) through Gli homogue Cl to antagonize hedgehog pathway TAN-1 Notch Translocation T-ALI. Signaling homologue MISCELLANEOUS SIGNALING BCL-2 Translocation B-cell lymphoma Apoptosis CBL Mu Cas NS-1 V Tyrosine- phosphorylated RING finger interact Ab1 CRK CT1010 ASV Adapted SH2/SH3 interact Ab1 DPC4 Tumor suppressor Pancreatic cancer TGF-.beta.-related signaling pathway MAS Transfection and Possible angiotensin Tumorigenicity receptor NCK Adaptor SH2/SH3 GUANINE NUCLEOTIDE EXCHANGERS AND BINDING PROTEINS BCR Translocated
with ABL Exchanger; protein in CML kinase DBL Transfection Exchanger GSP NF-1 Hereditary tumor Tumor suppressor RAS GAP Suppressor Neurofibromatosis OST Transfection Exchanger Harvey-Kirsten, N-RAS HaRat SV; Ki RaSV; Point mutations in many Signal cascade Balb-MoMuSV; human tumors Transfection VAV Transfection S112/S113; exchanger NUCLEAR PROTEINS AND TRANSCRIPTION FACTORS
BRCA1 Heritable suppressor Mammary Localization unsettled cancer/ovarian cancer BRCA2 Heritable suppressor Mammary cancer Function unknown ERBA Avian erythroblastosis thyroid hormone Virus receptor (transcription) ETS Avian E26 virus DNA binding EVII MuLV promotor AML Transcription factor Insertion FOS FBI/FBR murine 1 transcription factor osteosarcoma viruses with c-JUN GLI Amplified glioma Glioma Zinc finger; cubitus interruptus homologue is in hedgehog signaling pathway; inhibitory link PTC and hedgehog HMGG/LIM Translocation t(3:12) Lipoma Gene fusions high t(12:15) mobility group HMGI-C (XT-hook) and transcription factor LIM or acidic domain JUN ASV-17 Transcription factor AP-1 with FOS MLL/VHRX + ELI/MEN Translocation/fusion Acute myeloid leukemia Gene fusion of DNA- ELL with MLL binding and methyl Trithorax-like gene transferase MLL with ELI RNA pol II elongation factor

MYB Avian myeloblastosis DNA binding Virus MYC Avian MC29; Burkitt's lymphoma DNA binding with Translocation B-cell MAX partner; cyclin Lymphomas; promoter regulation; interact Insertion avian RB; regulate leukosis apoptosis Virus N-MYC Amplified Neuroblastoma L-MYC Lung cancer REL Avian NF-.kappa.B family Retriculoendotheliosis transcription factor Virus SKI Avian SKV770 Transcription factor Retrovirus VHL Heritable suppressor Von Hippel-Landau Negative regulator or syndrome elongin; transcriptional elongation complex WT-1 Wilm's tumor Transcription factor CELL CYCLE/DNA DAMAGE RESPONSE.sup.10-21 ATM Hereditary disorder Ataxia-telangiectasia Protein/lipid kinase homology; DNA damage response **upstream** in P53 pathway BCL-2 Translocation Follicular lymphoma Apoptosis FACC Point mutation Fanconi's anemia group C (predisposition leukemia FHIT Fragile site 3p14.2 Lung carcinoma Histidine triad-related diadenosine 5',3""- P.sup.1.multidot.p.sup.4 tetraphosphate asymmetric hydrolase hMLI/MutL HNPCC Mismatch repair; MutL homologue hMSH2/MutS HNPCC Mismatch repair; MutS homologue hPMS1 HNPCC Mismatch repair; MutL homologue hPMS2 HNPCC Mismatch repair; MutL homologue INK4/MTS1 Adjacent INK-4B at Candidate MTS1 p16 CDK inhibitor 9p21; CDK complexes suppressor and MLM melanoma gene INK4B/MTS2 Candidate suppressor p15 CDK inhibitor MDM-2 Amplified Sarcoma Negative regulator p53 p53 Association with SV40 Mutated >50% human Transcription factor; T antigen tumors, including checkpoint control; hereditary Li-Fraumeni apoptosis syndrome PRAD1/BCL1 Translocation with Parathyroid adenoma; Cyclin D Parathyroid hormone B-CLL or IgG RB Hereditary Retinoblastoma; Interact cyclin/cdk; Retinoblastoma; osteosarcoma; breast regulate E2F Association with many cancer; other sporadic transcription factor DNA virus tumor cancers

PGPUB-DOCUMENT-NUMBER: 20030078406

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030078406 A1

TITLE: Methods and compositions for DRM, a secreted protein with cell growth inhibiting activity

PUBLICATION-DATE: April 24, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Blair, Donald G.	Frederick	MD	US	
Clausen, Peter A.	Frederick	MD	US	
Topol, Lilia Z.	Frederick	MD	US	
Marx, Maria	L'Hay Les Roses		FR	
Calothy, Georges	Orsay		FR	

APPL-NO: 10/ 033717

DATE FILED: December 27, 2001

RELATED-US-APPL-DATA:

child 10033717 A1 20011227

parent continuation-of 09444066 19991119 US ABANDONED

child 09444066 19991119 US

parent continuation-of 09277407 19990326 US ABANDONED

non-provisional-of-provisional 60079440 19980326 US

US-CL-CURRENT: 536/23.5, 435/320.1 , 435/325 , 435/69.1 , 530/350

ABSTRACT:

The present invention provides an isolated nucleic acid encoding DRM protein, an isolated DRM polypeptide, and a fusion polypeptide comprising a DRM protein and a green fluorescent protein. The present invention also provides a method of arresting the growth of a cell, comprising administering to the cell an effective amount of DRM protein or an active fragment thereof; a method of inhibiting tumor cell growth, comprising administering to a tumor cell an effective amount of DRM protein or an active fragment thereof; and a method of treating a hyperproliferative cell disorder in a subject diagnosed with a hyperproliferative cell disorder, comprising administering to the subject an effective amount of DRM protein or an active fragment thereof, in a pharmaceutically acceptable carrier. In addition, the present invention provides a method of arresting growth of a cell, comprising administering to

the cell an effective amount of a nucleic acid encoding a DRM protein or an active fragment thereof, a method of inhibiting tumor cell growth, comprising administering to a tumor cell an effective amount of a nucleic acid encoding a DRM protein or an active fragment thereof; and a method of treating a hyperproliferative cell disorder in a subject diagnosed with a hyperproliferative cell disorder, comprising administering to a cell of the subject, in a pharmaceutically acceptable carrier, an effective amount of a nucleic acid encoding a DRM protein or an active fragment thereof, under conditions whereby the nucleic acid is expressed in the subject's cell.

[0001] This application claims priority to U.S. patent application Ser. No. 09/277,407, filed on Mar. 26, 1999, now abandoned, which claims priority to provisional application Serial No. 60/079,440 filed on Mar. 26, 1998, both of which are hereby incorporated herein by reference in their entirety.

---------- KWIC ---------

Detail Description Paragraph - DETX (31):

[0123] The characterization of a flat (non-transformed) revertant cell line, F-1, which was isolated from rat fibroblasts (DTM) transformed by the serine/threonine kinase oncogene mos has been previously reported (41). F-1 cells express high levels of v-mos-specific RNA and kinase activity, but fail to express characteristic transformed properties, including colony formation in soft agar and tumor formation in nude mice. Moreover, the revertants are resistant to re-transformation by v-mos and v-raf while they can be efficiently transformed by v-ras and, with a somewhat lower efficiency, v-**src**. The reversion and resistance to re-transformation correlated with the failure of the serine/threonine kinase oncogenes v-mos and v-raf to **activate** the MAP kinase pathway due to their inability to **activate** MEK-1 or MEK-2, the immediate **upstream activators** of MAP kinase.

PGPUB-DOCUMENT-NUMBER: 20030077284

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030077284 A1

TITLE: Product and method for treatment of conditions associated with receptor-desensitization

PUBLICATION-DATE: April 24, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Vilen, Barbara J.	Chapel Hill	NC	US	
Cambier, John C.	Denver	CO	US	

APPL-NO: 10/ 218670

DATE FILED: August 13, 2002

RELATED-US-APPL-DATA:

child 10218670 A1 20020813

parent continuation-of 09513024 20000225 US GRANTED

parent-patent 6503509 US

non-provisional-of-provisional 60121954 19990225 US

US-CL-CURRENT: 424/153.1

ABSTRACT:

Particular members of the multisubunit immune recognition receptor (MIRR) family of receptors, specifically, the B cell antigen receptor (BCR), the pre-B cell receptor (pre-BCR), the pro-B cell receptor (pro-BCR), Ig Fc receptors (FcR), and NK receptors, can be physically uncoupled from their associated transducers. The invention describes regulatory compounds and methods for mimicking such dissociation/destabilization for the purposes of receptor desensitization and for treatment of conditions in which receptor desensitization or alternatively, enhanced or prolonged receptor sensitization, is desirable. Compounds and methods for enhancing or prolonging receptor sensitization are also disclosed, as are methods for identifying regulatory compounds suitable for use in the present methods.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application claims priority under 35 U.S.C. .sctn. 119(e) from U.S. Provisional Application Serial No. 60/121,954, filed Feb. 25, 1999, entitled "Product and Method for Treatment of Conditions Associated with

Receptor-Desensitization." The entire disclosure of U.S. Provisional Application Serial No. 60/121,954 is incorporated herein by reference in its entirety.

---------- KWIC ---------

Detail Description Paragraph - DETX (76):

[0110] Previous studies of desensitized cells suggested that the defect in BCR signaling lies **upstream of src**-family kinase **activation,** possibly at the level of the receptor (Vilen et al., 1997). To address changes in BCR structure under conditions of receptor desensitization, the .mu.-heavy chain, Ig-.alpha. or Ig-.beta. were immunoprecipitated from desensitized K46.mu. cell lysates and the coprecipitated BCR components were quantitated. Briefly, a comparative analysis of mIg-Ig-.alpha./Ig-.beta. association in unstimulated K46.mu. cells, cells stimulated 1 hour with NP.sub.7BSA (500 mg/5.times.10.sup.6 cells/ml) or cells stimulated 1 hour with biotinylated b-7-6 (10 .mu.g/5.times.10.sup.6/ml) was performed. Biotinylated b-7-6 was prebound to unstimulated cells (10 .mu.g/5.times.10.sup.6 cells/ml) for 2 minutes at 4.degree. C. prior to lysis. FIG. 1 shows the results of the analysis as follows: Panel 1: Lanes 1 and 2 represent IgM and Ig-.alpha. immunoblots of anti-.mu. immunoprecipitates. Panel 2: Lanes 3 and 4 represent IgM, Ig-.beta. and Ig-.alpha. immunoblots of anti-Ig-.beta. immunoprecipitates. Panel 3: Lanes 5 and 6 represent IgM and Ig-.alpha. immunoblots of Ig-.alpha. immunoprecipitates. Panel 4: Lanes 7 and 8 represent IgM and Ig-.alpha. immunoblots of streptavidin immunoprecipitates.

PGPUB-DOCUMENT-NUMBER: 20030073163

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030073163 A1

TITLE: Libraries of expressible gene sequences

PUBLICATION-DATE: April 17, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Fernandez, Joseph Manuel	Carlsbad	CA	US	
Heyman, John Alastair	Cardiff-by-the-Sea	CA	US	
Hoeffler, James Paul	Carlsbad	CA	US	

APPL-NO: 10/ 003021

DATE FILED: November 14, 2001

RELATED-US-APPL-DATA:

child 10003021 A1 20011114

parent continuation-of 09285386 19990402 US PENDING

non-provisional-of-provisional 60096981 19980818 US

non-provisional-of-provisional 60080626 19980403 US

US-CL-CURRENT: 435/69.1, 435/183 , 435/193 , 435/320.1 , 435/325 , 435/6 , 536/23.2

ABSTRACT:

The invention described herein comprises libraries of expressible gene sequences. Such gene sequences are contained on plasmid vectors designed to endow the expressed proteins with a number of useful features such as affinity purification tags, epitope tags, and the like. The expression vectors containing such gene sequences can be used to transfect cells for the production of recombinant proteins. A further aspect of the invention comprises methods of identifying binding partners for the products of such expressible gene sequences.

RELATED APPLICATIONS

[0001] This application relies for priority on U.S. Provisional Application No. 60/080,626, filed Apr. 3, 1998, and U.S. Provisional Application No. 60/096,981, filed Aug. 18, 1998, each of which is hereby incorporated herein in its entirety.

--------- KWIC ---------

Detail Description Table CWU - DETL (19):
M221 E6 YLR142W proline oxidase (52.47/60) M84 C2 YLR144C Identified as an activity necessary for actin polymerization in permeabilized cells (85.72/90) M79 E4 YLR009W (22/32) M219 D4 YLR010C (17./6330) M219 D5 YLR011W (21.1/230) M219 D1 YLR015W (55.66/64) M219 D2 YLR016C (22.47/40) M219 D3 YLR017W Protein that regulates ADH2 gene expression (37.18/48) M219 E5 YLR019W (43.78/50) M219 E8 YLR022C (27.53/38) M80 A6 YLR026C Sed5p is a t-SNARE (soluble NSF attachment protein receptor) required in ER to Golgi transport. (37.43/25) M219 F5 YLR027C aspartate aminotransferase cytosolic (47.55/50) M79 F8 YLR029C Ribosomal protein RPL13A (YL10A) (rat L15) (22.47/30) M219 F8 YLR030W (29.04/40) M80 C2 YLR031W (20.57/32) M219 F3 YLR033W (55.33/55) M219 F6 YLR036C (22.46/33) M80 B10 YLR037C (13.67/13) M223 E1 YLR040C (24.67/38) M82 C6 YLR043C thioredoxin (11.46/12) M81 F7 YLR044C pyruvate decarboxylase (61.96/62) M82 D6 YLR051C (23.90/30) M222 G7 YLR053C (11.91/22) M82 C10 YLR054C (56.45/56) M223 B1 YLR055C transcription factor (66.35/70) M81 D2 YLR056W C-5 sterol desaturase (40.36/55) M81 H3 YLR057W (93.5/98) M81 D5 YLR058C serine hydroxymethyltransfe rase (51.62/55) M82 E6 YLR059C (29.62/30) M81 H7 YLR060W Phenylalanyl-tRNA synthetase alpha subunit cytoplasmic (65.56/65) M82 H8 YLR061W 402-755 (13.42/28) M222 A5 YLR066W signal peptidase subunit (20.45/34) M222 H3 YLR073C (22.03/34) M81 E5 YLR074C (18.39/28) M81 E5 YLR074C (18.39/28) M222 A6 YLR075W Ubiquinol- cytochrome C reductase complex subunit VI requiring protein (24.42/33) M222 A6 YLR075W Ubiquinol-cytochrome C reductase complex subunit VI requiring protein (24.42/33) M82 A8 YLR076C (15.43/16) M222 H7 YLR077W (64.24/67) M223 G5 YLR077W (64.24/60) M81 D1 YLR079W P40 inhibitor of Cdc28p-Clb5 protein kinase complex (31.45/50) M223 G3 YLR082C Smc4 protein member of SMC family (43.25/55) M222 B6 YLR083C integral membrane protein.backslash.p24a protein (73.40/90) M222 B4 YLR089C (65.25/65) M222 B4 YLR089C (65.25/65) M81 G5 YLR090W Homolog of E. coli DnaJ closely related to Ydj1p (50.6/60) M81 H6 YLR091W (32.34/40) M81 H6 YLR091W (32.34/40) M222 B8 YLR093C (27.64/39) M223 H2 YLR097C (37.87/52) M81 H5 YLR098C DNA binding **activator** (71.31/75) M222 D6 YLR099C (43.47/48) M82 C8 YLR100W (38.38/?) M82 C8 YLR100W (38.38/?) M81 A11 YLR102C (29.28/45) M82 F1 YLR103C omosomal DNA replication initiation protein (71.53/?) M222 E6 YLR107W (44.55/48) M222 D8 YLR109W (19.47/38) M81 G4 YLR113W mitogen-**activated** protein kinase (MAP kinase) (47.96/60) M81 A6 YLR114C (84.07/100) M81 A6 YLR114C (84.07/100) M223 D1 YLR119W suppressor of rnal-1 mutation (23.54/33) M222 D7 YLR124W (12.65/16) M222 F8 YLR125W (15.07/40) M82 A2 YLR127C APC (anaphase promoting complex) component (93.86/94) M82 D7 YLR131C **activator** of CUP1 expression (84.73/40) M222 E7 YLR132C (31.93/40) M221 A3 YLR137W (40.48/52) M84 C6 YLR139C (70.76/70) M86 G9 YLR141W **Upstream activation** factor subunit (40.04/55) M221 E6 YLR142W proline oxidase (52.47/60) M84 C2 YLR144C Identified as an activity necessary for actin polymerization in permeabilized cells (85.72/90) M221 F6 YLR150W (30.14/42) M255 H6 YLR151C (37.43/52) M84 G3 YLR153C acetyl-coenzyme A synthetase (75.16/75) M221 G4 YLR155C nitrogen catabolite-regulated cell-wall L- asparaginase II (39.85/50) M221 A2 YLR160C nitrogen catabolite- regulated cell-wall L- asparaginase II (39.85/50) M84 A8 YLR164W (18.59/19) M221 B1 YLR167W ubiquitin (16.83/16) M221 B2 YLR168C

(25.33/35) M86 G8 YLR172C S-adenosylmethionine (AdoMet)-dependent methyltransferase of diphthamide biosynthesis (33.03/40) M224 F1 YLR175W major low affinity 55 kDa Centromere.backslash./microtub ule binding protein (53.24/60) M221 C2 YLR176C (89.24/96) M86 H5 YLR178C suppressor of cdc25 (24.12/38) M221 H4 YLR179C (22.14/33) M221 F5 YLR180W S-adenosylmethionine synthetase (42.13/48) M221 E4 YLR186W (27.83/36) M84 A7 YLR187W (112.97/114) M84 D8 YLR188W ATP-binding cassette (ABC) transporter family member (76.56/76) M84 H9 YLR189C (131.81/?) M84 D11 YLR190W (54.12/70) M84 G1 YLR191W Peroxisomal membrane protein that contains **Src** homology 3 (SH3) domain (42.57/45) M221 F3 YLR193C (19.38/30) M84 B7 YLR195C N-myristoyl transferase (50.08/32) M84 A10 YLR197W homology to microtubule binding proteins and to X90565_5.cds (55.55/55) M221 D1 YLR199C (24.23/36) M221 E2 YLR200W Polypeptide 6 of a Yeast Non-native Actin Binding Complex homolog of a component of the bovine NABC complex (12.65/18) M84 D4 YLR201C (28.63/40) M84 C7 YLR203C Protein involved in maturation of COX1 and COB mRNA (47.99/48)

PGPUB-DOCUMENT-NUMBER: 20030068319

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030068319 A1

TITLE: Methods for inhibition of angiogenesis, tumor growth and metastasis by fully human anti-IL8 and anti-MUC18 in diverse types of tumors

PUBLICATION-DATE: April 10, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Bar-Eli, Menashe	Houston	TX	US	

APPL-NO: 10/ 104090

DATE FILED: March 22, 2002

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60278241 20010323 US

non-provisional-of-provisional 60334285 20011130 US

US-CL-CURRENT: 424/141.1, 424/145.1

ABSTRACT:

The present invention relates to methods of inhibiting hyperproliferative diseases. More specifically, it concerns treating a subject suffering from a hyperproliferative disease by administering an effective amount of a human anti-IL8 antibody composition and/or a human anti-MUC18 antibody composition such that the composition inhibits the disease.

BACKGROUND OF THE INVENTION

[0001] This application claims priority to U.S. Provisional Application No. 60/278,241, which was filed on Mar. 23, 2001 and to U.S. Provisional Application No. 60/334,285, which was filed on Nov. 13, 2001.

---------- KWIC ---------

Detail Description Table CWU - DETL (2):
2TABLE 1 Oncogenes Source Human Disease Function GROWTH FACTORS FGF family member HST/KS Transfection INT-2 MMTV promoter FGF family member Insertion INTI/WNTI MMTV promoter Factor-like Insertion SIS Simian sarcoma virus PDGF B RECEPTOR TYROSINE KINASES ERBB/HER Avian erythroblastosis

Amplified, deleted EGF/TGF-.alpha./ virus; ALV promoter Squamous cell Amphiregulin/ insertion; amplified Cancer; glioblastoma Hetacellulin receptor human tumors ERBB-2/NEU/HER-2 Transfected from rat Amplified breast, Regulated by NDF/ Glioblastomas Ovarian, gastric cancers Heregulin and EGF- Related factors FMS SM feline sarcoma virus CSF-1 receptor KIT HZ feline sarcoma virus MGF/Steel receptor Hematopoieis TRK Transfection from NGF (nerve growth human colon cancer Factor) receptor MET Transfection from Scatter factor/HGF human osteosarcoma Receptor RET Translocations and point Sporadic thyroid cancer; Orphan receptor Tyr mutations Familial medullary Kinase Thyroid cancer; Multiple endocrine Neoplasias 2A and 2B ROS URII avian sarcoma Orphan receptor Tyr Virus Kinase PDGF receptor Translocation Chronic TEL(ETS-like Myelomonocytic transcription factor)/ Leukemia PDGF receptor gene Fusion TGF-.beta. receptor Colon carcinoma Mismatch mutation Target NONRECEPTOR TYROSINE KINASES ABI. Abelson Mul.V Chronic myelogenous Interact with RB, RNA Leukemia translocation Polymerase, CRK, CBL with BCR FPS/FES Avian Fujinami SV; GA FeSV LCK Mul.V (murine leukemia **Src** family; T cell virus) promoter signaling; interacts insertion CD4/CD8 T cells **SRC** Avian Rous sarcoma Membrane-associated yr Virus kinase with signaling function; **activated** by receptor kinases YES Avian Y73 virus **Src** family; signaling SER/THR PROTEIN KINASES AKT AKT8 murine retrovirus Regulated by PI(3)K?; regulate 70-kd S6 k? MOS Maloney murine SV GVBD; cystostatic factor; MAP kinase kinase PIM-1 Promoter insertion Mouse RAF/MIL 3611 murine SV; MH2 Signaling in RAS avian SV Pathway MISCELLANEOUS CELL SURFACE APC Tumor suppressor Colon cancer Interacts with catenins DCC Tumor suppressor Colon cancer CAM domains E-cadherin Candidate tumor Breast cancer Extracellular homotypic Suppressor binding; intracellular interacts with catenins PTC/NBCCS Tumor suppressor and Nevoid basal cell cancer 12 transmembrane Drosophilia homology Syndrome (Gorline domain; signals Syndrome) through Gli homogue Cl to antagonize hedgehog pathway TAN-1 Notch Translocation T-ALI. Signaling homologue MISCELLANEOUS SIGNALING BCL-2 Translocation B-cell lymphoma Apoptosis CBL Mu Cas NS-1 V Tyrosine- Phosphorylated RING finger interact Ab1 CRK CT1010 ASV Adapted SH2/SH3 interact Ab1 DPC4 Tumor suppressor Pancreatic cancer TGF-.beta.-related signaling Pathway MAS Transfection and Possible angiotensin Tumorigenicity Receptor NCK Adaptor SH2/SH3 GUANINE NUCLEOTIDE EXCHANGERS AND BINDING PROTEINS BCR Translocated
with ABL Exchanger; protein in CML Kinase DBL Transfection Exchanger GSP NF-I Hereditary tumor Tumor suppressor RAS GAP Suppressor Neurofibromatosis OST Transfection Exchanger Harvey-Kirsten, HaRat SV; Ki RaSV; Point mutations in many Signal cascade N-RAS Balb-MoMuSV; Human tumors Transfection VAV Transfection S112/S113; exchanger NUCLEAR PROTEINS AND TRANSCRIPTION FACTORS
BRCA1 Heritable suppressor Mammary Localization unsettled Cancer/ovarian cancer BRCA2 Heritable suppressor Mammary cancer Function unknown ERBA Avian erythroblastosis thyroid hormone Virus receptor (transcription) ETS Avian E26 virus DNA binding EVII MuLV promotor AML Transcription factor Insertion FOS FBI/FBR murine 1 transcription factor osteosarcoma viruses with c-JUN GLI Amplified glioma Glioma Zinc finger; cubitus interruptus homologue is in hedgehog signaling pathway; inhibitory link PTC and hedgehog HMGI/LIM Translocation t (3:12) Lipoma Gene fusions high t (12:15) mobility group HMGI-C (XT-hook) and transcription factor LIM or acidic domain JUN ASV-17 Transcription factor AP-1 with FOS MLL/VHRX + Translocation/fusion Acute myeloid leukemia Gene fusion of DNA- ELI/MEN ELL with MLL binding and methyl

Trithorax-like gene transferase MLL with ELI RNA pol II elongation factor MYB Avian myeloblastosis DNA binding Virus MYC Avian MC29; Burkitt's lymphoma DNA binding with Translocation B-cell MAX partner; cyclin Lymphomas; promoter regulation; interact RB?; Insertion avianleukosis regulate apoptosis? Virus N-MYC Amplified Neuroblastoma L-MYC Lung cancer REL Avian NF-.kappa.B family Retriculoendotheliosis transcription factor Virus SKI Avian SKV770 Transcription factor Retrovirus VHL Heritable suppressor Von Hippel-Landan Negative regulator or Syndrome elongin; transcriptional elongation complex WT-1 Wilm's tumor Transcription factor CELL CYCLE/DNA DAMAGE RESPONSE ATM Hereditary disorder Ataxia-telangiectasia Protein/lipid kinase homology; DNA damage response **upstream** in P53 pathway BCL-2 Translocation Follicular lymphoma Apoptosis FACC Point mutation Fanconi's anemia group C (predisposition Leukemia MDA-7 Fragile site 3 p 14.2 Lung carcinoma Histidine triad-related diadenosine 5', 3""- tetraphosphate asymmetric hydrolase HMLI/MutL HNPCC Mismatch repair; MutL Homologue HMSH2/MutS HNPCC Mismatch repair; MutS Homologue HPMS1 HNPCC Mismatch repair; MutL Homologue HPMS2 HNPCC Mismatch repair; MutL Homologue INK4/MTS1 Adjacent INK-4B at Candidate MTS1 p16 CDK inhibitor 9 p 21; CDK complexes Suppressor and MLM Melanoma gene INK4B/MTS2 Candidate suppressor p15 CDK inhibitor MDM-2 Amplified Sarcoma Negative regulator p53 p53 Association with SV40 Mutated >50% human Transcription factor; T antigen Tumors, including checkpoint control; Hereditary Li-Fraumeni apoptosis Syndrome PRAD1/BCL1 Translocation with Parathyroid adenoma; Cyclin D Parathyroid hormone B-CLL or IgG RB Hereditary Retinoblastoma; Interact cyclin/cdk; Retinoblastoma; Osteosarcoma; breast regulate E2F Association with many Cancer; other sporadic transcription factor DNA virus tumor Cancers Antigens XPA Xeroderma Excision repair; photo- Pigmentosum; skin product recognition; Cancer predisposition zinc finger

PGPUB-DOCUMENT-NUMBER: 20030060425

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030060425 A1

TITLE: Immune modulation method using steroid compounds

PUBLICATION-DATE: March 27, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Ahlem, Clarence N.	San Diego	CA	US	
Frincke, James M.	San Diego	CA	US	
dos Anjos de Carvalho, Luis Daniel	Paio Pires Palmela	CA MD	PT PT	
Heggie, William	County Kildare	CA	IE	
Prendergast, Patrick T.	San Diego		US	
Reading, Christopher L.	Gaithersburg		US	
Thadikonda, Krupakar Paul	Oak Hills		US	
Vernon, Russell N.				

APPL-NO: 09/ 820483

DATE FILED: March 29, 2001

RELATED-US-APPL-DATA:

child 09820483 A1 20010329

parent continuation-in-part-of 09449184 19991124 US ABANDONED

child 09820483 A1 20010329

parent continuation-in-part-of 09414905 19991008 US ABANDONED

child 09820483 A1 20010329

parent continuation-in-part-of 09449004 19991124 US ABANDONED

child 09820483 A1 20010329

parent continuation-in-part-of 09535675 20000323 US PENDING

child 09820483 A1 20010329

parent continuation-in-part-of 09449042 19991124 US ABANDONED

child 09820483 A1 20010329

parent continuation-in-part-of 09675470 20000928 US PENDING

child 09820483 A1 20010329

parent continuation-in-part-of 09586673 20000601 US ABANDONED

child 09820483 A1 20010329

parent continuation-in-part-of 09586672 20000601 US ABANDONED

child 09820483 A1 20010329

parent continuation-in-part-of 09461026 19991215 US ABANDONED

non-provisional-of-provisional 60109924 19981124 US

non-provisional-of-provisional 60140028 19990616 US

non-provisional-of-provisional 60109923 19981124 US

non-provisional-of-provisional 60126056 19991019 US

non-provisional-of-provisional 60124087 19990311 US

non-provisional-of-provisional 60110127 19981127 US

non-provisional-of-provisional 60161453 19991025 US

non-provisional-of-provisional 60145823 19990727 US

non-provisional-of-provisional 60137745 19990603 US

non-provisional-of-provisional 60112206 19981215 US

non-provisional-of-provisional 60257071 20001220 US

US-CL-CURRENT: 514/26, 514/169 , 514/173 , 514/44 , 514/63 , 514/99

ABSTRACT:

The invention provides compositions comprising formula 1 steroids, e.g., 16.alpha.-bromo-3 .beta.-hydroxy-5.alpha.-androstan-17-one hemihydrate and one or more excipients, including compositions that comprise a liquid formulation comprising less than about 3% v/v water. The compositions are useful to make improved pharmaceutical formulations. The invention also provides methods of intermittent dosing of steroid compounds such as analogs of 16.alpha.-bromo-3.beta.-hydroxy-5.alpha.-androstan-17-one and compositions useful in such dosing regimens. The invention further provides compositions and methods to inhibit pathogen replication, ameliorate symptoms associated with immune dysregulation and to modulate immune responses in a subject using the compounds. The invention also provides methods to make and use these immunomodulatory compositions and formulations.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of: (1) pending U.S. application Ser. No. 09/449,184, filed Nov. 24, 1999, which claims priority to abandoned U.S. provisional application Ser. No. 60/109,924, filed Nov. 24, 1998, and (2) pending U.S. application Ser. No. 09/414,905, filed Oct. 8, 1999, which claims priority to abandoned U.S. provisional application Ser. No. 60/140,028, filed Jun. 16, 1999 and (3) pending U.S. application Ser. No. 09/449,004, filed Nov. 24, 1999, which claims priority to abandoned U.S. provisional application Ser. No. 60/109,923, filed Nov. 24, 1998, and (4) pending U.S. application Ser. No. 09/535,675, filed Mar. 23, 2000, which claims priority to abandoned U.S. provisional application Ser. No. 60/126,056, filed Mar. 23, 1999, and abandoned U.S. provisional application Ser. No. 60/124,087, filed Mar. 11, 1999 and (5) pending U.S. application Ser. No. 09/449,042, filed Nov. 24, 1999, which claims priority to abandoned U.S. provisional application Ser. No. 60/110,127, filed Nov. 27, 1998, and (6) pending U.S. application Ser. No. 09/675,470, filed Sep. 28, 2000, which claims priority to abandoned U.S. provisional application Ser. No. 60/161,453, filed Oct. 25, 1999, and (7) pending U.S. application Ser. No. 09/586,673, filed Jun. 1, 2000, which claims priority to abandoned U.S. provisional application Ser. No. 60/145,823, filed Jul. 27, 1999, and (8) pending U.S. application Ser. No. 09/586,672, filed Jun. 1, 2000, which claims priority to abandoned U.S. provisional application Ser. No. 60/137,745, filed Jun. 3, 1999, and (9) pending U.S. application Ser. No. 09/461,026, filed Dec. 15, 1999, which claims priority to abandoned U.S. provisional application Ser. No. 60/112,206, filed Dec. 15, 1998, all of which are incorporated herein by reference in their entireties.

---------- KWIC ---------

Detail Description Paragraph - DETX (653):

[0675] Additional exemplary mammalian and other transcription factors and receptors, including orphan nuclear receptors, their homologs, isoforms and co-factors (e.g., co-repressors, co-**activators**, transcription factors, gene promoter regions or sequences) and related molecules that the formula 1 compounds can directly or indirectly from complexes with, or modulate (detectably increase or decrease) the synthesis or one or more biological activities of, include steroidogenic factor-1 (SF-1), steroidogenic acute regulatory protein (StAR), chicken ovalbumin **upstream** promoter-transcription factor (COUP-TFI) and its mammalian homologs, silencing mediator for retinoid and thyroid hormone receptor (SMRT) and its mammalian homologs, sterol regulatory element binding protein (SREBP) 1a (SREBP-1a), SREBP-1c, SREPB-2, NF-E3, FKHR-L1, COUP-TFII and its mammalian homologs, I.kappa.B, I.kappa.B.alpha., AML-3, PEBP2.alpha.A1, Osf2, Cbfa1, RUNX2, steroid receptor coactivator-1 family (**SRC**-1, **SRC**-1/serum response factor), SET, nerve growth factor inducible protein B, StF-IT, NFAT, p300, CREB, CREB-binding protein (CPB), p300/CBP, p300/CPB-associated factor, SWI/SNF and their human and other homologs, BRG-1, OCT-1/OAF, AP1, Ets, androgen receptor associated protein 54 (ARA54), androgen receptor associated protein 55 (ARA55), androgen receptor associated protein 70 (ARA70), androgen receptor-interacting protein 3 (ARIP3), ARIP3/PIASx .alpha. complex, PIASx .alpha., Miz1, Miz1/PIASx .beta. complex , PIASx .beta., PIAS1, PIAS3, GBP, GBP/PIAS1 complex, RAC3/ACTR complex,

SRC-1.alpha., receptor interacting protein-140 (RIP-140), transcription factor **activator** protein-1, **activation** function-2, glucocorticoid receptor-interacting protein-1 (GRIP-1), receptor interacting protein-160 (RIP-160), suppressor of gal4D lesions (SUG-1), transcription intermediary factor-1 (TIF-1), transcription intermediary factor-2 (TIF-2), SMRT, N--CoR, N--CoA-1, p/CIP, p65 (RelA), heat shock proteins (HSP) such as HSP90 and HSP72, heat shock factor-1, Vpr encoded by the human immunodeficiency virus and its isoforms and homologs thereof, testicular orphan receptor TR2, thyroid hormone .alpha.1 (TR .alpha.1), retinoid X receptor .alpha., TR .alpha.1/RXR .alpha. heterodimer, direct repeat-4 thyroid hormone response element (DR4-TRE), an estrogen receptor (ER) such as ER.alpha. or ER.beta., estrogen receptor related .alpha. (ERR.alpha.), estrogen receptor related .beta. (ERR.beta.), steroid xenobiotic receptor (SXR), hepatocyte nuclear factor 4 (HNF-4), hepatocyte nuclear factor 3 (HNF-3), liver X receptors (LXRs), LXR.alpha., LXR.beta., estrogen receptor .alpha. (ER.alpha.), constitutive androstane receptor-.beta. (CAR-.beta.), RXR/CAR-.beta. heterodimer, short heterodimer partner (SHP), SHP/ER.alpha. heterodimer, estrogen receptor .beta., SHP/ER.beta. heterodimer, testicular orphan receptor TR4, TR2/TR4 heterodimer, pregnane X receptor (PXR) and isoforms, cytochrome P-450 monooxygenase 3A4 gene promoter region and isoforms, HNF-4/cytochrome P-450 monooxygenase 3A4 gene promoter region and isoforms complex, HIV-1 long terminal repeat (LTR), HIV-2 LTR, TR2/HIV-1 LTR complex, TR4/HIV-1 LTR complex, TR4/HIV-1 LTR complex, TR .alpha.1/TR4/HIV-1 LTR complex, TR2 isoforms (TR2-5, TR7, TR9, TR11), DAX-1, DAX-1/steroidogenic acute regulatory protein gene promoter region, RevErb, Rev-erbA .alpha., Rev-erb .beta., steroid receptor coactivator amplified in breast cancer (AIB 1), p300/CREB binding protein-interacting protein (p/CIP), thyroid hormone receptor (TR, T3R), thyroid hormone response elements (T3REs), constitutive androstane receptor (CAR), Xenopus xSRC-3 and mammalian (human) homologs, TAK1, TAK1/peroxisome proliferator-**activated** receptor .alpha. (PPAR.alpha.) complex, PPAR.alpha./RXR.alpha. complex, peroxisome proliferator-**activated** receptor .beta. (PPAR.beta.), peroxisome proliferator-**activated** receptor .gamma. (PPAR.gamma.), peroxisome proliferator-**activated** receptor .delta. (PPAR.delta.), farnesoid X receptor, TAK-1/RIP-140 complex, retinoic acid receptor (RAR), RAR.beta., TR4/RXRE complex, SF-1/steroid hydroxylase gene promoter region, SF-1/oxytocin gene promoter region, SF-1/ACTH receptor gene promoter region, rat Ear-2 and mammalian homologs, human TR3 orphan receptor (TR3), RLD-1, OR-1, androgen receptor, glucocorticoid receptor, estrogen receptor, progesterone receptor, mineralcorticoid receptor, aldosterone receptor, OR1, OR1/RXR.alpha. complex, TIF-1, CBP/P300 complex, TRIP1/SUG-1 complex, RIP-140, steroid receptor coactivator 1 (SRC1), SRC1.alpha./P160 complex and TIF-2/GRIP-1 complex, RAR/N--CoR/RIP13 complex, RAR/SMRT/TRAC-2 complex, and the DNARS 5' AGGTCANAGGTCA 3' or 5' TGCACGTCA 3'. The homologs, orthologs and isoforms of these transcription factors, receptors and other molecules are included among the molecules that the formula 1 compounds can modulate the synthesis or one or more biological activities of.

PGPUB-DOCUMENT-NUMBER: 20030059924

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030059924 A1

TITLE: Cloning of a novel inhibitor of antigen-receptor signaling by a retroviral-based functional screen

PUBLICATION-DATE: March 27, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Mancebo, Helen	Fremont	CA	US	
Holland, Sacha J.	San Francisco	CA	US	
Wu, Jun	Shanghai	CA	CN	
Liao, Charlene X.	Palo Alto		US	

APPL-NO: 10/ 043649

DATE FILED: January 10, 2002

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60260953 20010110 US

US-CL-CURRENT: 435/252.3

ABSTRACT:

The present invention provides compositions and methods for modulating leukocyte and/or platelet activation. Nucleic acids and proteins which are capable of modulating leukocyte and/or platelet activation are provided. Compositions and methods for the treatment of disorders related to leukocyte and/or platelet activation are also provided. Prophylactics and methods for the prevention of such disorders are also provided. Also provided are compositions and methods for diagnostic and prognostic determination of such disorders. Further provided are assays for the identification of bioactive agents capable of modulating leukocyte and/or platelet activation.

[0001] This application is a continuation in part of U.S. provisional application No. 60/260,953, filed Jan. 10, 2001, which is incorporated herein in its entirety by reference.

---------- KWIC ---------

Detail Description Paragraph - DETX (248):

[0295] SLIM associates with tyrosine phosphorylated proteins following antigen receptor engagement. Signaling through the TCR or BCR results in a

rapid increase in tyrosine phosphorylation of numerous intracellular proteins, initiated by **Src** family and Syk/ZAP70 kinase **activation**. These early signaling events ultimately result in transcriptional **activation,** upregulation of surface antigens, and other lymphocyte effector functions. Adapter proteins play an important intermediary role in integrating **upstream** signals to produce biological function. In order to investigate the nature of SLIM signaling complexes, epitope-tagged versions of SLIM, SLIM-myr, or SLIM-DC were stably introduced into BJAB cells. All three proteins became associated with a number of tyrosine phosphorylated proteins following BCR stimulation (FIG. 5A), demonstrating that SLIM indeed participates in BCR signaling pathways. Interestingly, a prominent phosphoprotein of approximately 110 kD was absent in the immunoprecipitates of SLIM-DC (FIG. 5A), which we subsequently identified as the RING finger ubiquitin ligase Cbl (FIG. 5B). Cbl has been previously shown to be a negative regulator in TCR signaling pathway and to constitutively interact with the C-terminal region of SLAP as demonstrated in both a yeast two hybrid system and mammalian cells. However, the association between SLIM and Cbl in B cells was inducible following antigen receptor stimulation, suggesting SLIM and SLAP may utilize different mechanisms to recruit other signaling partners. It would be possible for SLIM to function as an inhibitory adapter by either recruiting a negative regulator into the signaling pathway and/or by directly blocking the function of a positive regulator. Our results suggest that SLIM functions via the former mechanism in antigen receptor signaling cascades.

PGPUB-DOCUMENT-NUMBER: 20030045499

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030045499 A1

TITLE: Dendritic cells transduced with a wild-type self gene elicit potent antitumor immune responses

PUBLICATION-DATE: March 6, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Gabrilovich, Dmitry	Aurora	IL	US	
Carbone, David	Franklin	TN	US	
Chada, Sunil	Missouri City	TX	US	
Mhashilkar, Abner	Houston	TX	US	

APPL-NO: 10/ 216346

DATE FILED: August 9, 2002

RELATED-US-APPL-DATA:

child 10216346 A1 20020809

parent division-of 09526320 20000315 US PENDING

non-provisional-of-provisional 60124482 19990315 US

non-provisional-of-provisional 60124388 19990315 US

US-CL-CURRENT: 514/44

ABSTRACT:

The present invention relates to immunotherapy methods for treating hyperproliferative disease or pathogen-induced diseases in humans. More specifically, the invention is directed, in one embodiment, to methods for treating a subject with a hyperproliferative disease in which the expression of a self gene is upregulated in hyperproliferative cells. In another embodiment, an adenoviral expression construct comprising a self gene under the control of a promoter operable in eukaryotic cells is intradermally administered to said hyperproliferative cells. In another embodiment of the present invention, a pathogen-induced disease in which the pathogen gene expression is increased or altered, is treated by intradermally administered a pathogen gene under the control of a promoter operable in eukaryotic cells. The present invention thus provides immunotherapies for treating hyperproliferative and pathogen diseases by attenuating the natural immune systems CTL response against hyperproliferative cells or overexpressing mutant p53 antigens.

---------- KWIC ---------

Detail Description Table CWU - DETL (1):

1TABLE 1 ONCOGENES Gene Source Human Disease Function Growth Factors.sup.1 HST/KS Transfection FGF family member INT-2 MMTV promoter FGF family member insertion INTI/WNTI MMTV promoter Factor-like insertion SIS Simian sarcoma PDGF B virus Receptor Tyrosine Kinases.sup.1,2 ERBB/HER Avian erythro- Amplified, EGF/TGF-.alpha./ blastosis virus; deleted squamous amphiregulin/ ALV promoter cell cancer; hetacellulin receptor insertion; glioblastoma amplified human tumors ERBB-2/ Transfected from Amplified breast, Regulated by NDF/ NEU/HER-2 rat glioblatoms ovarian, gastric heregulin and EGF- cancers related factors FMS SM feline CSF-1 receptor sarcoma virus KIT HZ feline MGF/Steel receptor sarcoma virus hematopoieis TRK Transfection NGF (nerve growth from human factor) receptor colon cancer MET Transfection Scatter factor/HGF from human receptor osteosarcoma RET Translocations Sporadic thyroid Orphan receptor Tyr and point cancer; familial kinase mutations medullary thyroid cancer; multiple endocrine neoplasias 2A and 2B ROS URII avian Orphan receptor Tyr sarcoma virus kinase PDGF Translocation Chronic TEL (ETS-like receptor myclomonocytic transcription factor)/ leukemia PDGF receptor gene fusion TGF-.beta. Colon carcinoma receptor mismatch mutation target NONRECEPTOR TYROSINE KINASES.sup.1 ABI Abelson Mul. V Chronic Interact with RB, myelogenous RNA polymerase, leukemia CRK, CBL translocation with BCR FPS/FES Avian Fujinami SV; GA FeSV LCK Mul. V (murine **Src** family; T cell leukemia virus) signaling; interacts promoter CD4/CD8 T cells insertion **SRC** Avian Rous Membrane- sarcoma virus associated Tyr kinase with signaling function; **activated** by receptor kinases YES Avian Y73 **Src** family; virus signaling SER/THR PROTEIN KINASES.sup.1 AKT AKT8 murine Regulated by retrovirus PI(3)K?; regulate 70-kd S6 k? MOS Maloney murine GVBD; cystostatic SV factor; MAP kinase kinase PIM-1 Promoter insertion mouse RAF/MIL 3611 murine SV; Signaling in RAS MH2 avian SV pathway MISCELLANEOUS CELL SURFACE.sup.1 APC Tumor suppressor Colon cancer Interacts with catenins DCC Tumor suppressor Colon cancer CAM domains E-cadherin Candidate tumor Breast cancer Extracellular suppressor homotypic binding; intracellular interacts with catenins PTC/NBCCS Tumor suppressor Nevoid basal cell 12 transmembrane and Drosophilia cancer syndrome domain; signals homology (Gorline through Gli syndrome) homogue CI to antagonize hedgehog pathway TAN-1 Translocation T-ALL Signaling? Notch homologue MISCELLANEOUS SIGNALING.sup.1,3 BCL-2 Translocation B-cell lymphoma Apoptosis CBL Mu Cas NS-1 V Tyrosine- phosphorylated RING finger interact Ab1 CRK CT1010 ASV Adapted SH2/SH3 interact Ab1 DPC4 Tumor suppressor Pancreatic cancer TGF-.beta.-related signaling pathway MAS Transfection and Possible angiotensin tumorigenicity receptor NCK Adaptor SH2/SH3 GUANINE NUCLEOTIDE EXCHANGERS AND BINDING PROTEINS.sup.3,4 BCR Translocated with Exchanger; protein ABL in CML kinase DBL Transfection Exchanger GSP NF-I Hereditary tumor Tumor suppressor RAS GAP suppressor neurofibromatosis OST Transfection Exchanger Harvey- HaRat SV; Ki Point mutations Signal cascade Kirsten, RaSV; Balb- in many human N-RAS MoMuSV; tumors transfection VAV Transfection S112/S113; exchanger NUCLEAR PROTEINS AND TRANSCRIPTION FACTORS.sup.1,5-9 BRCA1 Heritable Mammary cancer/ Localization suppressor ovarian cancer unsettled BRCA2 Heritable Mammary cancer Function unknown suppressor ERBA Avian erythro- thyroid hormone blastosis virus receptor

(transcription) ETS Avian E26 virus DNA binding EVII MuLV promotor AML Transcription factor insertion FOS FBI/FBR murine 1 transcription osteosarcoma factor with c-JUN viruses GLI Amplified glioma Glioma Zinc finger; cubitus interruptus homologue is in hedgehog signaling pathway; inhibitory link PTC and hedgehog HMGG/LIM Translocation Lipoma Gene fusions high t(3:12) t(12:15) mobility group HMGI-C (XT-hook) and transcription factor LIM or acidic domain JUN ASV-17 Transcription factor AP-1 with FOS MLL/ Translocation/ Acute myeloid Gene fusion of VHRX + fusion ELL with leukemia DNA-binding and ELI/MEN MLL trithorax- methyl transferase like gene MLL with ELI RNA pol II elongation factor MYB Avian myelo- DNA binding blastosis virus MYC Avian MC29; Burkitt's DNA binding with translocation lymphoma MAX partner; B-cell cyclin regulation; lymphomas; interact RB?; promoter regulate apoptosis? insertion avian leukosis virus N-MYC Amplified Neuroblastoma L-MYC Lung cancer REL Avian retriculo- NF-.kappa.B family endotheliosis transcription factor virus SKI Avian SKV770 Transcription factor retrovirus VHL Heritable Von Hippel- Negative regulator suppressor Landau syndrome or elongin; trans- criptional elongation complex WT-1 Wilm's tumor Transcription factor CELL CYCLE/DNA DAMAGE RESPONSE.sup.10-21 ATM Hereditary Ataxia- Protein/lipid kinase disorder telangiectasia homology; DNA damage response **upstream** in P53 pathway BCL-2 Translocation Follicular Apoptosis lymphoma FACC Point mutation Fanconi's anemia group C (predisposition leukemia FHIT Fragile site Lung carcinoma Histidine triad-3p14.2 related diadenosine 5',3""-P.sup.1p.sup.4 tetra- phosphate asymmetric hydrolase hMLI/MutL HNPCC Mismatch repair; MutL homologue hMSH2/ HNPCC Mismatch repair; MutS MutS homologue hPMS1 HNPCC Mismatch repair; MutL homologue hPMS2 HNPCC Mismatch repair; MutL homologue INK4/MTS1 Adjacent INK-4B Candidate MTS1 p16 CDK inhibitor

PGPUB-DOCUMENT-NUMBER: 20030032596

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030032596 A1

TITLE: Inhibition of the Src kinase family pathway as a method of treating HBV infection and hepatocellular carcinoma

PUBLICATION-DATE: February 13, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Schneider, Robert J.	New York	NY	US	
Klein, Nicola	New York	NY	US	

APPL-NO: 10/ 196344

DATE FILED: July 15, 2002

RELATED-US-APPL-DATA:

child 10196344 A1 20020715

parent continuation-of 08874430 19970613 US GRANTED

parent-patent 6420338 US

US-CL-CURRENT: 514/12, 514/262.1 , 514/44

ABSTRACT:

The present invention relates to therapeutic protocols and pharmaceutical compositions designed to target HBx mediated activation of Src kinase, members of the Src tyrosine kinase family and components of the Src kinase family signal transduction pathways for the treatment of HBV infection and related disorders and diseases, such as HCC. The invention further relates to pharmaceutical compositions for the treatment of HBV infection targeted to HBx and its essential activities required to sustain HBV replication. The invention is based, in part, on the Applicants' discovery that activation of Src kinase signaling cascades play a fundamental role in mammalian hepadnavirus replication. Applicants have demonstrated that HBx mediates activation of the Src family of kinases and that this activation is a critical function provided by HBx for mammalian hepadnavirus replication.

--------- KWIC ---------

Detail Description Paragraph - DETX (4):

[0040] The present invention encompasses a variety of protocols to inhibit

HBV replication and infection, including but not limited to: (1) protocols which target and inhibit HBx expression or inhibit the essential activities of HBx which may lead to **activation of the Src** kinase signaling cascades; (2) protocols which target and inhibit **upstream** effectors of the **Src** family of kinases, which may or may not be **activated** by HBx, but are required for **activation of Src** kinase signaling cascades; and (3) protocols which target and inhibit **Src** kinase family members, **Src-activated** enzymes and downstream effectors of **Src** kinases and their signal transduction pathways that are essential for viral replication.

Detail Description Paragraph - DETX (32):

[0062] Gene therapy approaches may also be used in accordance with the present invention to inhibit the **activation of Src** kinase and components of its signaling cascade. The gene therapy approaches described herein may also be applied to HBx, **Src** family of kinases and **upstream** and downstream effectors of the **Src** kinase signaling cascade in accordance with the present invention. Among the compounds which may disrupt the activities of HBx and its **activation of the Src** kinase signaling cascade are antisense, ribozyme, triple helix molecules, SELEX RNAs and dominant-negative mutants. Such molecules are designed to inhibit the expression of the target gene in HBV-infected host cells. Techniques for the production and use of antisense, ribozyme, triple helix and/or SELEX RNAs are well known to those of skill in the art and can be designed with respect to the CDNA sequence of **Src** kinase and components of the **Src** kinase signaling cascade.

PGPUB-DOCUMENT-NUMBER: 20030031665

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030031665 A1

TITLE: Anti-CD26 monoclonal antibodies as therapy for diseases associated with cells expressing CD26

PUBLICATION-DATE: February 13, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Dang, Nam Hoang	Houston	TX	US	
Morimoto, Chikao	Tokyo	MA	JP	
Schlossman, Stuart	Newton Centre		US	

APPL-NO: 10/ 143553

DATE FILED: May 10, 2002

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60290531 20010511 US

US-CL-CURRENT: 424/141.1, 424/144.1 , 435/334 , 435/70.21

ABSTRACT:

Therapeutic methods comprising administering anti-CD26 antibodies for the prevention and treatment of cancers and immune diseases associated with expressing CD26 are provided. The invention describes various types of anti-CD26 antibodies and modes of administration.

[0001] The present application claims priority to co-pending U.S. patent application Ser. No. 60/290,531, filed May 11, 2001. The entire text of the above-referenced disclosure is specifically incorporated by reference herein without disclaimer.

---------- KWIC ---------

Detail Description Table CWU - DETL (2):

2TABLE 1 Gene Source Human Disease Function Growth Factors FGF family member HST/KS Transfection INT-2 MMTV promoter FGF family member Insertion INTI/WNTI MMTV promoter Factor-like Insertion SIS Simian sarcoma virus PDGF B Receptor Tyrosine Kinases ERBB/HER Avian erythroblastosis Amplified, deleted EGF/TGF-.alpha. virus; ALV promoter squamous cell Amphiregulin insertion; amplified cancer; glioblastoma Hetacellulin receptor human tumors ERBB-2/NEU/ Transfected from rat Amplified breast, Regulated by NDF/ HER-2

Glioblastomas ovarian, gastric cancers Heregulin and EGF- Related factors FMS SM feline sarcoma virus CSF-1 receptor KIT HZ feline sarcoma virus MGF/Steel receptor Hematopoieis TRK Transfection from NGF (nerve growth human colon cancer Factor) receptor MET Transfection from Scatter factor/HGF human osteosarcoma Receptor RET Translocations and point Sporadic thyroid cancer; Orphan receptor Tyr mutations familial medullary Kinase thyroid cancer; multiple endocrine neoplasias 2A and 2B ROS URII avian sarcoma Orphan receptor Tyr Virus Kinase PDGF receptor Translocation Chronic TEL(ETS-like Myelomonocytic transcription factor)/ Leukemia PDGF receptor gene Fusion TGF-.beta. receptor Colon carcinoma mismatch mutation target NONRECEPTOR TYROSINE KINASES ABI. Abelson Mul. V Chronic myelogenous Interact with RB, RNA leukemia translocation polymerase, CRK, With BCR CBL FPS/FES Avian Fujinami SV; GA FeSV LCK Mul. V (murine leukemia **Src** family; T-cell virus) promoter signaling; interacts insertion CD4/CD8 T-cells **SRC** Avian Rous sarcoma Membrane-associated Virus Tyr kinase with signaling function; **activated** by receptor kinases YES Avian Y73 virus **Src** family; signaling SER/THR PROTEIN KINASES AKT AKT8 murine retrovirus Regulated by PI(3)K?; regulate 70-kd S6 k? MOS Maloney murine SV GVBD; cystostatic factor; MAP kinase kinase PIM-1 Promoter insertion Mouse RAF/MIL 3611 murine SV; MH2 Signaling in RAS avian SV Pathway MISCELLANEOUS CELL SURFACE.sup.1 APC Tumor suppressor Colon cancer Interacts with catenins DCC Tumor suppressor Colon cancer CAM domains E-cadherin Candidate tumor Breast cancer Extracellular homotypic Suppressor binding; intracellular interacts with catenins PTC/NBCCS Tumor suppressor and Nevoid basal cell cancer 12 trausmembrane Drosophilia homology syndrome (Gorline domain; signals syndrome) through Gli homogne Cl to antagonize hedgehog pathway TAN-1 Notch Translocation T-ALI. Signaling? homologne MISCELLANEOUS SIGNALING BCL-2 Translocation B-cell lymphoma Apoptosis CBL Mu Cas NS-1 V Tyrosine- Phosphorylated RING finger interact Ab1 CRK CT1010 ASV Adapted SH2/SH3 interact Ab1 DPC4 Tumor suppressor Pancreatic cancer TGF-.beta.-related signaling Pathway MAS Transfection and Possible angiotensin Tumorigenicity Receptor NCK Adaptor SH2/SH3 GUANINE NUCLEOTIDE EXCHANGERS AND BINDING PROTEINS BCR Translocated
with ABL Exchanger; protein in CML Kinase DBL Transfection Exchanger GSP NF-1 Hereditary tumor Tumor suppressor RAS GAP Suppressor neurofibromatosis OST Transfection Exchanger Harvey-Kirsten, HaRat SV; Ki RaSV; Point mutations in many Signal cascade N-RAS Balb-MoMuSV; human tumors Transfection VAV Transfection S112/S113; exchanger NUCLEAR PROTEINS AND TRANSCRIPTION FACTORS
BRCA1 Heritable suppressor Mammary Localization unsettled cancer/ovarian cancer BRCA2 Heritable suppressor Mammary cancer Function unknown ERBA Avian erythroblastosis thyroid hormone Virus receptor (transcription) ETS Avian E26 virus DNA binding EVII MuLV promotor AML Transcription factor Insertion FOS FBI/FBR murine 1 transcription factor osteosarcoma viruses with c-JUN GLI Amplified glioma Glioma Zinc finger; cubitus interruptus homologue is in hedgehog signaling pathway; inhibitory link PTC and hedgehog HMGI/LIM Translocation t(3:12) Lipoma Gene fusions high t(12:15) mobility group HMGI-C (XT-hook) and transcription factor LIM or acidic domain JUN ASV-17 Transcription factor AP-1 With FOS MLL/VHRX + Translocation/fusion Acute myeloid leukemia Gene fusion of DNA- ELI/MEN ELL with MLL binding and methyl Trithorax-like gene transferase MLL with ELI RNA pol II elongation factor MYB Avian myeloblastosis DNA binding Virus MYC Avian MC29; Burkitt's lymphoma DNA binding with Translocation B-cell MAX partner; cyclin

Lymphomas; promoter regulation; interact Insertion avian RB?; regulate leukosis apoptosis? Virus N-MYC Amplified Neuroblastoma L-MYC Lung cancer REL Avian NF-.kappa.B family Retriculoendotheliosis transcription factor Virus SKI Avian SKV770 Transcription factor Retrovirus VHL Heritable suppressor Von Hippel-Landau Negative regulator or syndrome elongin; transcriptional elongation complex WT-1 Wilm's tumor Transcription factor CELL CYCLE/DNA DAMAGE RESPONSE.sup.10-21 ATM Hereditary disorder Ataxia-telangiectasia Protein/lipid kinase homology; DNA damage response **upstream** in P53 pathway BCL-2 Translocation Follicular lymphoma Apoptosis FACC Point mutation Fanconi's anemia group C (predisposition leukemia MDA-7 Fragile site 3p14.2 Lung carcinoma Histidine triad-related diadenosine 5', 3""- tetraphosphate asymmetric hydrolase hMLI/MutL HNPCC Mismatch repair; MutL Homologue hMSH2/MutS HNPCC Mismatch repair; MutS Homologue hPMS1 HNPCC Mismatch repair; MutL Homologue hPMS2 HNPCC Mismatch repair; MutL Homologue INK4/MTS1 Adjacent INK-4B at Candidate MTS1 p16 CDK inhibitor 9p21; CDK complexes suppressor and MLM melanoma gene INK4B/MTS2 Candidate suppressor p15 CDK inhibitor MDM-2 Amplified Sarcoma Negative regulator p 53 p 53 Association with SV40 Mutated >50% human Transcription factor; T antigen tumors, including checkpoint control; hereditary Li-Fraumeni apoptosis syndrome PRAD1/BCL1 Translocation with Parathyroid adenoma; Cyclin D Parathyroid hormone B-CLL or IgG RB Hereditary Retinoblastoma; Interact cyclin/cdk; Retinoblastoma; osteosarcoma; breast regulate E2F Association with many cancer; other sporadic transcription factor DNA virus tumor cancers Antigens XPA xeroderma Excision repair; photo- pigmentosum; skin product recognition; cancer predisposition zinc finger

PGPUB-DOCUMENT-NUMBER: 20030023385

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030023385 A1

TITLE: Statistical analysis method for classifying objects

PUBLICATION-DATE: January 30, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Lazaridis, Emmanuel	Tampa	FL	US	

APPL-NO: 09/ 913498

DATE FILED: August 16, 2001

PCT-DATA:
APPL-NO: PCT/US01/03616
DATE-FILED: Feb 5, 2001
PUB-NO:
PUB-DATE:
371-DATE:
102(E)-DATE:

US-CL-CURRENT: 702/19, 435/6 , 514/44

ABSTRACT:

An information computational method for classifying multivariate datasets to identify latent (unobservable) properties of members of a sample, which properties are then used for classification. The method comprises a novel combination of statistical and fuzzy logic methods whereby the latent classes of each object are identified according to the formula:
.function.(.sub.j.sub..sub.1.sub., . . . , j.sub..sub.K).vertline.[(j.sub.-k.epsilon.S.sub.km.sub..sub.jk].sub.k=1.sup.K.about.G[h(k,j.sub.k,[[S.sub.-km].sub.m=1.sup.M.sup..sub.k].sub.k=1.sup.K)]
wherein k.epsilon.[1, . . . , K] indexes the directions of the multidimensional space; j.sub.k.epsilon.[1, . . . , N.sub.k] identifies an object in direction k; N.sub.k is the number of objects in principal direction k; .sub.j.sub..sub.1.sub., . . . , j.sub..sub.K is a vector of one or more observations on a set of objects [j.sub.1, . . . , j.sub.K]; m.epsilon.[1, . . . , M.sub.k] indexes latent classes in direction k with M.sub.k being the number of latent classes in direction k; S.sub.km is a latent class m in direction k; G[.multidot.] is a specified univariate or multivariate distribution; f(.multidot.) and g(.multidot.) are specified functions; and the method calculates the likelihood that each object of interest belongs to each identified latent class. The invention addresses a variety of informatics problems, particularly in the field of biology, and permits a user to make

reasonable inferences about underlying cause-effect relationships, such as the underlying biology of gene-expression patterns.

---------- KWIC ---------

Detail Description Paragraph - DETX (30):

[0064] Colorectal cancer is a common, deadly disease with 129,400 new cases and 56,600 deaths projected for 1999 in the United States. While surgical resection of localized tumors may be curative, the vast majority of deaths are linked to the metastatic spread of tumor cells. Sporadic colorectal cancer is known to arise from an accumulation of multiple, sequential somatic genetic changes within a cell, each of which likely has complex effects on gene expression. This invention addresses the problem of identifying molecular fingerprints relating to colorectal cancer metastasis as a means of substantially improving diagnostic and prognostic capacities, and potentially elucidating new mechanisms underlying the metastatic process Sporadic colon cancer is the result of multiple, sequential somatic genetic alterations, which likely affect numerous pathways. Early epidemiological studies predicted that at least 5-6 genetic events would be required to generate a colon cancer. It is now appreciated that somatic mutations in the APC gene are common to the vast majority of colorectal cancers. Its mutation is the first step towards carcinogenesis, a step that leads to a multitude of complex downstream pathway effects. Its alteration often leads to truncation of its product, with subsequent downstream effects on multiple APC partners including catenin, p130Cas, E-Cadherin, and T cell factor-4 (Tcf-4). More specifically, it has been determined that mutations in APC or in catenin increase the activity of the catenin/Tcf-4 complex, leading to overexpression of c-MYC and cyclin D1 with subsequent promotion of neoplastic growth. APC mutation can now be related to the downstream effects of c-MYC on gene transcription and translation. For example, recent studies have demonstrated that MYC activities are modulated by a network of bHLH-Zip proteins with MAX at the center of the network. Whereas MYC-MAX complexes **activate** transcription, MAD-MAX complexes repress transcription. For this reason, mRNA/protein levels of critical genes may increase or decrease in response to specific **upstream** stimuli. Like APC mutation, mutation of RAS is also thought to be an early event with downstream effects on signaling pathways involving many partners including Raf, MEK, and MAPK. Recently, Ras has been implicated in the Myc pathway by the finding that Ras enhances the accumulation of Myc activity by stabilizing a protein with an otherwise short half-life. Subsequent to APC and/or RAS mutations, genetic events associated with tumor progression are thought to include the alteration of genes such as DCC, DPC4, and P53. The instant inventors have recently described a mutation of **SRC** in codon 531 which may contribute to the aggressiveness of advanced tumors with metastatic potential. Each of these somatic genetic events burden affected cells by triggering multiple downstream changes in gene transcription and translation, thereby increasing the capacity of the cell to progress and develop deadly metastatic potential. The challenge is to identify the critical components of each pathway affected by these genetic alterations and to characterize the network connections.

PGPUB-DOCUMENT-NUMBER: 20030017573

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030017573 A1

TITLE: Polymerase kappa compositions and methods thereof

PUBLICATION-DATE: January 23, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Friedberg, Errol C.	Dallas	TX	US	
Gerlach, Valerie	Branford	CT	US	
Feaver, William J.	Branford	CT	US	

APPL-NO: 09/ 971101

DATE FILED: October 4, 2001

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60238289 20001004 US

US-CL-CURRENT: 435/226, 435/320.1 , 435/325 , 435/69.1 , 536/23.2

ABSTRACT:

The present invention concerns compositions and methods involving mammalian polymerase kappa, an enzyme with limited fidelity and moderate processivity. Methods of modulating polymerase kappa activity, such as inhibiting or reducing its activity, as a means of effecting a cancer treatment or preventative agent are provided, both by itself and in combination with other anti-cancer therapies. Also described are methods of screening involving assaying for polymerase kappa activity or expression, in addition to methods of screening for modulators of polymerase kappa to identify anti-cancer compounds.

[0001] This application claims the priority of U.S. Provisional Application Ser. No. 60/238,289, filed Oct. 4, 2000, the entire disclosure of which is specifically incorporated herein by reference. The government may own rights in the present invention pursuant to grant numbers CA 75733 and CA69029 from the National Cancer Institute.

---------- KWIC ---------

Detail Description Table CWU - DETL (10):

10TABLE 9 Oncogenes Gene Source Human Disease Function Growth Factors HST/KS Transfection FGF family member INT-2 MMTV promoter FGF family member Insertion INTI/WNTI MMTV promoter Factor-like Insertion SIS Simian sarcoma

virus PDGF B Receptor Tyrosine Kinases ERBB/HER Avian erythroblastosis Amplified, deleted EGF/TGF-.alpha./ virus; ALV promoter Squamous cell Amphiregulin/ insertion; amplified Cancer; glioblastoma Hetacellulin receptor human tumors ERBB-2/NEU/HER-2 Transfected from rat Amplified breast, Regulated by NDF/ Glioblastomas Ovarian, gastric Heregulin and EGF- cancers Related factors FMS SM feline sarcoma virus CSF-1 receptor KIT HZ feline sarcoma virus MGF/Steel receptor Hematopoieis TRK Transfection from NGF (nerve growth human colon cancer Factor) receptor MET Transfection from Scatter factor/HGF human osteosarcoma Receptor RET Translocations and point Sporadic thyroid cancer; Orphan receptor Tyr mutations familial medullary Kinase thyroid cancer; multiple endocrine neoplasias 2A and 2B ROS URII avian sarcoma Orphan receptor Tyr Virus Kinase PDGF receptor Translocation Chronic TEL(ETS-like Myelomonocytic transcription factor)/ Leukemia PDGF receptor gene Fusion TGF-.beta. receptor Colon carcinoma mismatch mutation target NONRECEPTOR TYROSINE KINASES ABI. Abelson Mul.V Chronic myelogenous Interact with RB, RNA leukemia translocation polymerase, CRK, with BCR CBL FPS/FES Avian Fujinami SV;GA FeSV LCK Mul.V (murine leukemia **Src** family; T cell virus) promoter signaling; interacts insertion CD4/CD8 T cells **SRC** Avian Rous sarcoma Membrane-associated Virus Tyr kinase with signaling function; **activated** by receptor kinases YES Avian Y73 virus **Src** family; signaling SER/THR PROTEIN KINASES AKT AKT8 murine retrovirus Regulated by PI(3)K?; regulate 70-kd S6 k? MOS Maloney murine SV GVBD; cystostatic factor; MAP kinase kinase PIM-1 Promoter insertion Mouse RAF/MIL 3611 murine SV; MH2 Signaling in RAS avian SV Pathway MISCELLANEOUS CELL SURFACE APC Tumor suppressor Colon cancer Interacts with catenins DCC Tumor suppressor Colon cancer CAM domains E-cadherin Candidate tumor Breast cancer Extracellular homotypic Suppressor binding; intracellular interacts with catenins PTC/NBCCS Tumor suppressor and Nevoid basal cell cancer 12 transmembrane Drosophilia homology syndrome (Gorline domain; signals syndrome) through Gli homogue Cl to antagonize hedgehog pathway TAN-1 Notch Translocation T-ALI. Signaling homologue MISCELLANEOUS SIGNALING BCL-2 Translocation B-cell lymphoma Apoptosis CBL Mu Cas NS-1 V Tyrosine- Phosphorylated RING finger interact Abl CRK CT1010ASV Adapted SH2/SH3 interact Abl DPC4 Tumor suppressor Pancreatic cancer TGF-.beta.-related signaling Pathway MAS Transfection and Possible angiotensin Tumorigenicity Receptor NCK Adaptor SH2/5H3 GUANINE NUCLEOTIDE EXCHANGERS AND BINDING PROTEINS BCR Translocated
with ABL Exchanger; protein in CML Kinase DBL Transfection Exchanger GSP NF-1 Hereditary tumor Tumor suppressor RAS GAP Suppressor neurofibromatosis OST Transfection Exchanger Harvey-Kirsten, N-RAS HaRat SV; Ki RaSV; Point mutations in many Signal cascade Balb-MoMuSV; human tumors Transfection VAV Transfection S112/S113; exchanger NUCLEAR PROTEINS AND TRANSCRIPTION FACTORS
BRCA1 Heritable suppressor Mammary Localization unsettled cancer/ovarian cancer BRCA2 Heritable suppressor Mammary cancer Function unknown ERBA Avian erythroblastosis Thyroid hormone Virus receptor (transcription) ETS Avian E26 virus DNA binding EVII MuLV promotor AML Transcription factor Insertion FOS FBI/FBR murine Transcription factor osteosarcoma viruses with c-JUN GLI Amplified glioma Glioma Zinc finger; cubitus interruptus homologue is in hedgehog signaling pathway; inhibitory link PTC and hedgehog HMGI/LIM Translocation t(3:12) Lipoma Gene fusions high t(12:15) mobility group HMGI-C (XT-hook) and transcription factor LIM or acidic domain JUN ASV-17 Transcription factor AP-1 with FOS MLL/VHRX + ELI/MEN Translocation/fusion

Acute myeloid leukemia Gene fusion of DNA- ELL with MLL binding and methyl Trithorax-like gene transferase MLL with ELI RNA p01 II elongation factor MYB Avian myeloblastosis DNA binding Virus MYC Avian MC29; Burkitt's lymphoma DNA binding with Translocation B-cell MAX partner; cyclin Lymphomas; promoter regulation; interact Insertion avian RB?; regulate leukosis apoptosis? Virus N-MYC Amplified Neuroblastoma L-MYC Lung cancer REL Avian NF-.kappa.B family Retriculoendotheliosis transcription factor Virus SKI Avian SKV77O Transcription factor Retrovirus VHL Heritable suppressor Von Hippel-Landau Negative regulator or syndrome elongin; transcriptional elongation complex WT-1 Wilm's tumor Transcription factor CELL CYCLE/DNA DAMAGE RESPONSE ATM Hereditary disorder Ataxia-telangiectasia Protein/lipid kinase homology; DNA damage response **upstream** in P53 pathway BCL-2 Translocation Follicular lymphoma Apoptosis FACC Point mutation Fanconi's anemia group C(predisposition leukemia FHIT Fragile site 3p14.2 Lung carcinoma Histidine-triad-related diadenosine 5',3 ""- P.sup.1.p.sup.4tetraphosphate asymmetric hydrolase hMLI/MutL HNPCC Mismatch repair; MutL Homologue HMSH2/MutS HNPCC Mismatch repair; MutS Homologue HPMS1 HNPCC Mismatch repair; Mutl Homologue hPMS2 HNPCC Mismatch repair; MutL Homologue INK4/MTS1 Adjacent INK-4B at Candidate MTS1 p16 CDK inhibitor 9p21; CDK complexes suppressor and MLM melanoma gene INK4B/MTS2 Candidate suppressor p15 CDK inhibitor MDM-2 Amplified Sarcoma Negative regulator p53 p53 Association with SV40 Mutated >50% human Transcription factor; T antigen tumors, including checkpoint control; hereditary Li-Fraumeni apoptosis syndrome PRAD1/BCL1 Translocation with Parathyroid adenoma; Cyclin D Parathyroid hormone B-CLL or IgG RB Hereditary Retinoblastoma; Interact cyclin/cdk; Retinoblastoma; osteosarcoma; breast regulate E2F Association with many cancer; other sporadic transcription factor DNA virus tumor cancers Antigens XPA xeroderma Excision repair; photo- pigmentosum; skin product recognition; cancer predisposition zinc finger

PGPUB-DOCUMENT-NUMBER: 20020151060

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020151060 A1

TITLE: PEI: DNA vector formulations for in vitro and in vivo gene delivery

PUBLICATION-DATE: October 17, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Cristiano, Richard J.	Pearland	TX	US	
Yamashita, Motoyuki	Kochi City		JP	

APPL-NO: 09/ 962922

DATE FILED: September 25, 2001

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60235237 20000925 US

non-provisional-of-provisional 60235635 20000926 US

US-CL-CURRENT: 435/455, 424/486 , 514/44

ABSTRACT:

The present invention relates generally to the fields of nucleic acid transfection. More particularly, it concerns novel polycation:nucleic acid compositions, methods of preparation of such compositions and methods of transfecting cells with such compositions.

[0001] This application claims the priority of U.S. Provisional Patent Application Ser. No. 60/235,237, filed Sep. 25, 2000 and U.S. Provisional Patent Application Ser. No. 60/235,635, filed Sep. 26, 2000, both of which disclosures are specifically incorporated herein by reference in their entirety.

---------- KWIC ---------

Detail Description Table CWU - DETL (6):
6TABLE 4 Oncogenes Gene Source Human Disease Function Growth Factors's.sup.1 FGF family member HST/KS Transfection INT-2 MMTV promoter FGF family member Insertion INTI/WNTI MMTV promoter Factor-like Insertion SIS Simian sarcoma PDGF B virus Receptor Tyrosine Kinases.sup.1,2 ERBB/HER Avian Amplified, deleted EGF/TGF-.alpha./ erythroblastosis Squamous cell

amphiregulin/ Virus; ALV Cancer; hetacellulin promoter glioblastoma receptor Insertion; amplified Human tumors ERBB-2/NEU/HER-2 Transfected from rat Amplified breast, Regulated by NDF/ Glioblatoms Ovarian, gastric heregulin and cancers EGF- related factors FMS SM feline sarcoma CSF-1 receptor virus KIT HZ feline sarcoma MGF/Steel receptor virus hematopoieis TRK Transfection from NGF (nerve growth Human colon factor) receptor cancer MET Transfection from Scatter factor/HGF Human receptor osteosarcoma RET Translocations and Sporadic thyroid Orphan receptor Tyr point mutations cancer; kinase Familial medullary Thyroid cancer; multiple endocrine neoplasias 2A and 2B ROS URII avian sarcoma Orphan receptor Tyr Virus kinase PDGF receptor Translocation Chronic TEL(ETS-like Myclomonocytic transcription Leukemia factor)/ PDGF receptor gene fusion TGF-.beta.receptor Colon carcinoma Mismatch mutation Target NONRECEPTOR TYROSINE KINASES.sup.1 ABI. Abelson Mul.V Chronic Interact with RB, myelogenous RNA Leukemia polymerase, CRK, translocation CBL With BCR FPS/FES Avian Fujinami SV;GA FeSV LCK Mul.V (murine **Src** family; T cell leukemia signaling; interacts Virus) promoter CD4/CD8 T cells Insertion **SRC** Avian Rous Membrane- sarcoma associated Tyr Virus kinase with signaling function; **activated** by receptor kinases YES Avian Y73 virus **Src** family; signaling SER/THR PROTEIN KINASES.sup.1 AKT AKT8 murine Regulated by retrovirus PI(3)K?; regulate 70-kd S6 k? MOS Maloney murine SV GVBD; cystostatic factor; MAP kinase kinase PIM-1 Promoter insertion Mouse RAF/MIL 3611 murine SV; Signaling in RAS MH2 pathway avian SV MISCELLANEOUS CELL SURFACE.sup.1 APC Tumor suppressor Colon cancer Interacts with catenins DCC Tumor suppressor Colon cancer CAM domains E-cadherin Candidate tumor Breast cancer Extracellular Suppressor homotypic binding; intracellular interacts with catenins PTC/NBCCS Tumor suppressor Nevoid basal cell 12 transmembrane and cancer domain; signals Drosophilia Syndrome (Gorline through Gli homology Syndrome) homogue CI to antagonize hedgehog pathway TAN-1 Notch Translocation T-ALI. Signaling? homologue MISCELLANEOUS SIGNALING.sup.1,3 BCL-2 Translocation B-cell lymphoma Apoptosis CBL Mu Cas NS-1 V Tyrosine- phosphorylated RING finger interact Abl CRK CT1010 ASV Adapted SH2/SH3 interact Abl DPC4 Tumor suppressor Pancreatic cancer TGF-.beta.-related signaling pathway MAS Transfection and Possible angiotensin Tumorigenicity receptor NCK Adaptor SH2/SH3 GUANINE NUCLEOTIDE EXCHANGERS AND BINDING PROTEINS.sup.3,4 BCR Translocated with Exchanger; protein ABL kinase in CML DBL Transfection Exchanger GSP NF-1 Hereditary tumor Tumor suppressor RAS GAP Suppressor Neurofibromatosis OST Transfection Exchanger Harvey-Kirsten, N- HaRat SV; Ki Point mutations in Signal cascade RAS RaSV; many Balb-MoMuSV; human tumors Transfection VAV Transfection S112/S113; exchanger NUCLEAR PROTEINS AND TRANSCRIPTION FACTORS.sup.1,5-9 BRCA1 Heritable suppressor Mammary Localization cancer/ovarian unsettled cancer BRCA2 Heritable suppressor Mammary cancer Function unknown ERBA Avian Thyroid hormone erythroblastosis receptor Virus (transcription) ETS Avian E26 virus DNA binding EVII MuLV promotor AML Transcription factor Insertion FOS FBI/FBR murine 1 transcription osteosarcoma factor viruses with c-JUN GLI Amplified glioma Glioma Zinc finger; cubitus interruptus homologue is in hedgehog signaling pathway; inhibitory link PTC and hedgehog HMGI /LIM Translocation Lipoma Gene fusions high t(3:12) mobility group t(12:15) HMGI-C (XT- hook) and transcription factor LIM or acidic domain JUN ASV-17 Transcription factor AP-1 with FOS MLL/VHRX+ Translocation/fusion Acute myeloid Gene fusion of ELI/MEN ELL with MLL leukemia DNA- Trithorax-like gene binding and methyl transferase MLL with ELI RNA pol II elongation factor MYB Avian DNA binding myeloblastosis Virus MYC Avian MC29; Burkitt's

lymphoma DNA binding with Translocation B- MAX partner; cell cyclin Lymphomas; regulation; interact promoter RB?; regulate Insertion avian apoptosis? leukosis Virus N-MYC Amplified Neuroblastoma L-MYC Lung cancer REL Avian NF-.kappa.B family transcription factor Retriculoendothelio sis Virus SKI Avian SKV770 Transcription factor Retrovirus VHL Heritable suppressor Von Hippel-Landau Negative regulator Syndrome or elongin; transcriptional elongation complex WT-1 Wilm's tumor Transcription factor CELL CYCLE/DNA DAMAGE RESPONSE.sup.10-21 ATM Hereditary disorder Ataxia- Protein/lipid kinase telangiectasia homology; DNA damage response **upstream** in P53

PGPUB-DOCUMENT-NUMBER: 20020150954

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020150954 A1

TITLE: Compositions and methods for identifying agents which modulate PTEN function and PI-3 kinase pathways

PUBLICATION-DATE: October 17, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Durden, Donald L.	Indianapolis	IN	US	

APPL-NO: 09/ 870379

DATE FILED: May 30, 2001

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60208437 20000530 US

non-provisional-of-provisional 60274167 20010308 US

US-CL-CURRENT: 435/7.23, 514/12 , 514/152 , 514/27 , 514/283 , 514/449

ABSTRACT:

Methods are provided for the identification, biochemical characterization and therapeutic use of agents which impact PTEN, p53, PI-kinase and AKT mediated cellular signaling.

[0001] This invention claims priority under 35 U.S.C. .sctn.119(e) to U.S. Provisional Application Nos. 60/208,437 and 60/274,167 filed May 30, 2000 and Mar. 8, 2001 respectively. The entire disclosures of each of the above-identified applications is incorporated by reference herein.

---------- KWIC ---------

Detail Description Paragraph - DETX (143):

[0167] It is well known that Fc.gamma. receptor crosslinking induces the tyrosine phosphorylation of the adapter protein, Cbl (Park, R. K., et al., (1996) J. Immumology 160:5018). To determine if phagocytic signaling events lead to the phosphorylation of Cbl, the degree of Cbl phosphorylation was assessed before and after induction of phagocytosis. To investigate the role of specific kinases in this phosphorylation event, dominant negative Syk and the **Src** family kinase inhibitor PP1 were utilized to inhibit the activity of these enzymes. The results demonstrated that Cbl was phosphorylated on

tyrosine residues following induction of phagocytosis and this phosphorylation event was abrogated by PP1 (FIGS. 11A and 11B, compare lanes 2-3 to 5-6). This effect was dose dependent (data not shown), as was the effect of PP1 on inhibition of Fc.gamma. receptor-mediated phagocytosis (FIG. 11A). Interestingly, dominant negative Syk inhibited Cbl tyrosine phosphorylation to a lesser extent but completely abrogated the phagocytic response. Interestingly, both PP1 and dominant negative Syk suppressed the basal tyrosine phosphorylation levels of Cbl in vivo. These data suggested that the catalytic activity of the **Src** family kinases and the capacity of Syk to dock with the ITAM receptor were both required for Cbl phosphorylation in response to phagocytic stimuli and that these two events were required for phagocytosis. The dominant negative Syk would not be expected to alter the **upstream** activity of **Src** family kinases and hence **Src** mediated phosphorylation of Cbl was not altered to the same extent. The data provided support for a signaling cascade in which Syk functions downstream of **Src and upstream** of Cbl and other effectors associated with Cbl such as the p85 subunit of PI-3 kinase. The data demonstrated that **Src** family kinases mediated the phosphorylation of Cbl in a Syk kinase independent manner in vivo. The data also revealed that **Src** family kinases and Syk were required for phagocytosis mediated by the downstream **activation** of PI-3 kinase.

PGPUB-DOCUMENT-NUMBER: 20020150567

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020150567 A1

TITLE: NOVEL GRB2 ASSOCIATING POLYPEPTIDES AND NUCLEIC ACIDS ENCODING THEREFOR

PUBLICATION-DATE: October 17, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Pot, David A.	San Francisco	CA	US	
Williams, Lewis T.	Tiburon	CA	US	
Jefferson, Anne Bennett	University City	MO	US	
Majerus, Philip W.	University City	MO	US	

APPL-NO: 09/ 969528

DATE FILED: October 1, 2001

RELATED-US-APPL-DATA:

child 09969528 A1 20011001

parent division-of 09418540 19991014 US GRANTED

parent-patent 6296848 US

child 09418540 19991014 US

parent continuation-of 08560005 19951117 US GRANTED

parent-patent 6001354 US

US-CL-CURRENT: 424/94.6, 435/196 , 435/320.1 , 435/325 , 435/69.1 , 536/23.2

ABSTRACT:

The present invention generally relates to novel GRB2 associating proteins and nucleic acids which encode these protein. In particular, these novel proteins possess inositol polyphosphate 5-phosphatase and phosphatidylinositol 5-phosphatase activities, important in growth factor mediated signal transduction. As such, the proteins, nucleic acids encoding the proteins, cells capable of expressing these nucleic acids and antibodies specific for these proteins will find a variety of uses in a variety of screening, therapeutic and other applications.

---------- KWIC ---------

Detail Description Paragraph - DETX (7):

. [0038] PtdIns(3,4,5)P.sub.3 in particular, is the product of phosphatidyl inositol 3-kinase ("PI3 kinase"), an important agonist **activated** signaling protein, stimulated in growth factor mediated signal transduction. PI3-kinase is known to be involved in the regulation of cell growth and oncogenic transformation (Cantley et al., Cell, 64:1657 (1993)). Upon growth factor receptor stimulation, the wild-type PI3-kinase is **activated** and can phosphorylate phosphatidylinositol ("PtdIns") at the 3' position of the inositol ring. These phosphatidylinositol 3-phosphates are candidate second messenger molecules. The PI3-kinase enzyme is found associated with receptor protein tyrosine kinases such as PDGF-R-.beta., CSF-1 receptor, Insulin receptor and IGF-1 receptor as well as non-receptor tyrosine kinase oncogenes, e.g., **src,** gag-abl and fyn. Studies on mutants of platelet-derived growth factor (PDGF) receptor have shown that PI3-kinase is a key mediator of PDGF-mediated mitogenic signaling (Fantl et al., Cell, 69:413 (1992); Valius et al., ibid., 73:321 (1993)). PDGF-R mutants that are unable to bind PI3-kinase are also unable to induce a mitogenic response after growth factor stimulation and unable to **activate** p21c-Ras (Ras). These data indicate that PI3-kinase acts **upstream** of Ras in PDGF-stimulated signaling. Studies also indicate that the PI3-kinase product, PtdIns(3,4,5)P.sub.3 is not the final product produced during the initial phases of signaling, indicating further processing of this signaling molecule. Stephens, et al., Nature 351:33-39 (1991), Hawkins, et al., Nature 358:157-159 (1992).

US-PAT-NO: 6518063

DOCUMENT-IDENTIFIER: US 6518063 B1

TITLE: Osf2/Cbfa1 nucleic acids and methods of use therefor

DATE-ISSUED: February 11, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Ducy; Patricia	Houston	TX	N/A	N/A
Karsenty; Gerard	Houston	TX	N/A	N/A

APPL-NO: 09/ 086663

DATE FILED: May 29, 1998

PARENT-CASE:

The present application is a continuing application of U.S. Provisional Application Serial No. 60/080,189 filed Mar. 24, 1998, which was a continuing application of U.S. Provisional Application Serial No. 60/048,430 filed May 29, 1997, the entire contents of each of which is specifically incorporated herein by reference in its entirety.

US-CL-CURRENT: 435/325, 435/252.3 , 435/320.1 , 536/23.5

ABSTRACT:

Disclosed are methods and compositions comprising a novel osteoblast-specific transcription factor designated Osf2/Cbfa1. Also disclosed are nucleic acid segments encoding this polypeptide derived from human cell lines, and the use of these polynucleotides in a variety of diagnostic and therapeutic applications. Methods, compositions, kits, and devices are also provided for identifying compounds which are inhibitors of osteoblast differentiation, and identifying Osf2/Cbfa1 polynucleotides and polypeptides in a sample. Also disclosed are nucleic acid compositions comprising an Osf2 promoter, and the use of the promoter in heterologous and homologous gene transcription and protein production.

30 Claims, 54 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 37

---------- KWIC ---------

Detailed Description Text - DETX (438):

primary culture," Mol. Cell Biol., 10:689-695, 1990. Rodan and Martin, "Role of the osteoblasts in hormonal control of bone resorption. A hypothesis," Calcif. Tissue Int., 33:349-352, 1981. Rodan et al. "Pathophysiology of osteoporosis," Principles of Bone Biology. Bilezikian et al. eds. San Diego, Calif. Academic Press. pp. 979-990. 1996. Rose, Anal. Chem., 65(24):3545-3549, 1993. Rosenfeld et al., "Adenovirus-mediated transfer of a recombinant .alpha.1-antitrypsin gene to the lung epithelium in vivo," Science, 252:431434, 1991. Rosenfeld et al., "In vivo transfer of the human cystic fibrosis transmembrane conductance regulator gene to the airway epithelium," Cell, 68:143-155, 1992. Rossert, Chen, Eberspaecher, Smith, de Chrombrugghe, "Identification of a minimal sequence of the mouse pro-.alpha.1 (I) collagen promoter that confers high-level osteoblast expression in transgenic mice and that binds a protein selectively present in osteoblasts," Proc. Natl. Acad. Sci. USA, 93:1027-1031, 1996. Rossi et al., Aids Res. Hum. Retrovir., 8:183, 1992. Roux et al., "A versatile and potentially general approach to the targeting of specific cell types by retroviruses: Application to the infection of human cells by means of major histocompatibility complex class I and class II antigens by mouse ecotropic murine leukemia virus-derived viruses," Proc. Natl. Acad. Sci. USA, 86:9079-9083, 1989. Ruskowski et al., Cancer, 80(12 Suppl):2699-2705, 1997. Sadowski and Ptashne, "A vector for expressing GAL4 (1-147) fusion in mammalian cells," Nucl. Acids Res., 17:7539, 1989. Sambrook, Fristch, Maniatis, "Molecular Cloning: A Laboratory Manual," C. Nolan, ed., Cold Spring Harbor Laboratory Press, Cold Spring Harbor, N.Y., 1989. Sampath, Maliakal, Hauschka, Jones, Sasak, Tucker, White, Coughlin, Tucker, Pang, Corbett, Ozkaynak, Oppermann, Rueger, "Recombinant human osteogenic protein-1 (hOP-1) induces new bone formation in vivo with a specific activity comparable with natural bovine osteogenic protein and stimulates osteoblast proliferation and differentiation in vitro," J. Biol. Chem., 267:20352-20362, 1992. Sarver et al., Science, 247:1222-1225, 1990. Sasaki, Yagi, Bronson, Tominaga, Matsunashi, Deguchi, Tani, Kishimoto, Komori, "Absence of fetal liver hematopoiesis in mice deficient in transcriptional coactivator core binding factor .beta.," Proc. Natl. Acad. Sci. USA, 93:12359-12363, 1996. Satake, Nomura, Yamagushi-Iwai, Takahama, Hashimoto, Niki, Kitamura, Ito, "Expression of the runt domain-encoding PEBP2.alpha. genes in T cells during thymic development," Mol. Cell. Biol., 15:1662-1670, 1995. Sauer, Hansen, Tjian, "Multiple TAF.sub.IIS directing synergistic **activation** of transcription," Science, 270:1783-1788, 1995. Saville and Collins, Cell, 61:685-696, 1990. Saville and Collins, Proc. Natl. Acad. Sci. USA, 88:8826-8830, 1991. Scanlon et al., Proc. Natl. Acad. Sci. USA, 88:10591-10595, 1991. Scaringe et al., Nuc. Acids Res., 18:5433-5441, 1990. Sculier et al., "Pilot study of amphotericin B entrapped in sonicated liposomes in cancer patients with fuingal infections," J. Cancer Clin. Oncol., 24(3):527-538, 1988. Seeger et al., Biotechniques, 23(3):512-517, 1997. Segal, "Biochemical Calculations" 2nd Edition. John Wiley & Sons, New York, 1976. Seitz et al., "Effect of transforming growth factor .beta. on parathyroid hormone receptor binding and cAMP formation in rat osteosarcoma cells," J. Bone Min. Res., 7:541-546, 1992. Selby and Selby, "Gamma-ray-induced dominant mutations that cause skeletal abnormalities in mice. II. Description of proved mutations," Mut. Res., 51:199-236, 1978. Selvamurugan, Pearmen, Chou, Pulumati, Brown, Baumann, Angel, Partridge, "Parathyroid hormone regulates the rodent collagenase gene through the AP-1 site together with an **upstream** regulatory element," Abstr. T460, Abstr. 18th

Annu. Meet. Am. Soc. Bone Min. Res., p. S414, 1996. Shimell et al., "The Drosophila dorsal-ventral patterning gene tolloid is related to human bone morphogenetic protein 1," Cell, 67:469-481, 1991. Sillence et al., "Animal model: skeletal abnormalities in mice with cleidocranial dysplasia," Am. J. Med. Genet., 27:75-85, 1987. Simeone, Daga, Calabi, "Expression of runt in the mouse embryo," Dev. Dyn., 203(1):61-70, 1995. Soriano, Montgomery, Geske, Bradley, "Targeted disruption of the c-src proto-oncogene leads to osteopetrosis in mice," Cell, 64(4):693-702, 1991. Speck and Stacy, "A new transcription factor family associated with human leukemias," Crit. Rev. Euk. Gene Exp., 5:337-364, 1995. Spiegelman and Flier, "Adipogenesis and obesity: rounding out the big picture," Cell, 87:377-389, 1996. Spoerel and Kafatos, "Identification of genomic sequences corresponding to cDNA clones," Methods Enzymol., 152:588-597, 1987. Stetsenko, Lubyako, Potapov, Azhikina, Sverdlov, Tetrahedron Lett., 37:3571-3574, 1996. Stinchcomb, Struhl, Davis, "Isolation and characterization of a yeast chromosomal replicator," Nature, 282(5734):39, 1979. Stratford-Perricaudet and Perricaudet, "Gene transfer into animals: the promise of adenovirus," p. 51-61, In: Human Gene Transfer, Eds, O. Cohen-Haguenauer and M. Boiron, Editions John Libbey Eurotext, France, 1991. Stratford-Perricaudet et al., "Evaluation of the transfer and expression in mice of an enzyme-encoding gene using a human adenovirus vector," Hum. Gene Ther., 1:241-256, 1990. Strauss, "Preparation of genomic DNA from mammalian tissue," In: Current Protocols in Molecular Biology, Boston, John Wiley and Sons, Ausubel et al. Eds., Vol. 1, pp. 221-223, 1994. Suda, Takahashi, Martin, "Modulation of osteoclast differentiation," Endocrine Rev., 13:66-80, 1992. Sudo, Kodama, Amagai, Yamamoto, Kasai, "In vitro differentiation and calcification of a new clonal osteogenic cell line derived from newborn mouse calvaria," J. Cell Biol., 96:191-198, 1983. Sundin, Busse, Rogers, Gudas, Eichele, "Region-specific expression in early chick and mouse embryo of Ghox-lab and Hox 1.6, vertebrate homeobox-containing genes related to Drosophila labial," Development, 108:47-58, 1990. Tabin, "Retinoids, homeoboxes, and growth factors: toward molecular models for limb development," Cell, 66:199-217, 1991. Tairaet al., Nucl. Acids Res., 19:5125-5130, 1991. Taylor and Jones. "Multiple new phenotypes induced in 10T1/2 and 3T3 cells treated by 5-azacytidine," Cell, 17:771-779, 1979. Temin, "Retrovirus vectors for gene transfer: Efficient integration into and expression of exogenous DNA in vertebrate cell genome," In: Gene Transfer, Kucherlapati (ed.), New York: Plenum Press, pp. 149-188, 1986. Thiede, Bayerdorffer, Blasczyk, Wittig, Neubauer, Nucleic Acids Res., 24:983-984, 1996. Thisted, Just, Petersen, Hyldig-Nielsen, Godtfredsen, Cell Vision, 3:358-363, 1996. Thomson et al., Tetrahedron, 51:6179-6194, 1995. Tomanin et al., Gene, 193(2):129-140, 1997. Tomic et al., Nucl. Acids Res., 12:1656, 1990. Tontonoz et al., "Stimulation of adipogenesis in fibroblasts by PPAR 2, a lipid-activated transcription factor," Cell, 79:1147-1156, 1994. Top et al., "Immunization with live types 7 and 4 adenovirus vaccines. II. Antibody response and protective effect against acute respiratory disease due to adenovirus type 7," J. Infect. Dis., 124:155-160, 1971. Towler, Bennett, Rodan, "Activity of the rat osteocalcin basal promoter in osteoblastic cells is dependent upon homeodomain and CP1 binding motifs," Mol. Endocrinol., 8:614-624, 1994. Tsai and Gergen, "Gap gene properties of the pair-rule gene runt during Drosophila segmentation," Development, 120:1671-1683, 1994. Tschumper and Carbon, "Sequence of a yeast DNA fragment containing a chromosomal replicator and the TRP1 gene," Gene, 10(2):157-166, 1980. Tubulekas et al., Gene, 190(1):191-195, 1997. Tur-Kaspa et al., "Use of electroporation to introduce biologically active foreign genes

into primary rat hepatocytes," Mol. Cell Biol., 6:716-718, 1986. Ulmann, Will, Breipohl, Langner, Ryte, Angew. Chem., Int. Ed. Engl., 35:2632-2635, 1996. Upender et al., Biotechniques, 18:29-31, 1995. Usman and Cedergren, TIBS, 17:34, 1992. Usman et al., J. Am. Chem. Soc., 109:7845-7854, 1987. Van Dyke, Sirito, Sawadogo, "Single-step purification of bacterially expressed polypeptides containing an oligo-histidine domain," Gene, 111:99-104, 1992. Varmus et al., "Retroviruses as mutagens: Insertion and excision of a nontransforming provirus alter the expression of a resident transforming provirus," Cell, 25:23-36, 1981. Ventura et al., Nucl. Acids Res., 21:3249-3255, 1993. Veselkov, Demidov, Nielsen, Frank-Kamenetskii, Nucl. Acids Res., 24:2483-2487, 1996. Vickers, Griffith, Ramasamy, Risen, Freier, Nucl. Acids Res., 23:3003-3008, 1995. Vignery and Baron, "Dynamic histomorphometry of alveolar bone remodeling in the adult rat," Anat. Rec., 196(2):191-200, 1980. Voss and Rosenfeld, "Anterior pituitary development: short tales from dwarf mice," Cell. 70:527-530, 1992. Wagner, Matteucci, Lewis, Gutierrez, Moulds, Froehler, "Antisense gene inhibition by oligonucleotides containing C-5 propyne pyrimidines," Science, 260(5113):1510-1513, 1993. Wagner, Zatloukal, Cotten, Kirlappos, Mechtler, Curiel, Birnstiel, "Coupling of adenovirus to transferrin-polylysine/DNA complexes greatly enhances receptor-mediated gene delivery and expression of transfected genes," Proc. Natl. Acad. Sci. USA, 89(13):6099-6103, 1992. Walker et al., Proc. Natl. Acad. Sci. USA, 89(1):392-396, 1992. Wang et al., "Bone and haematopoietic defects in mice lacking c-fos," Nature, 360(6406):741-745, 1992. Wang et al., Methods enzymol., 288:38-55, 1997. Wang, J. Am. Chem. Soc., 118:7667-7670, 1996. Wang, Stacy, Binder, Marin-Padilla, Sharpe, Speck, "Disruption of the Cbfa2 gene causes necrosis and hemorrhaging in the central nervous system and blocks definitive hematopoiesis," Proc. Natl. Acad. Sci. USA, 93:3444-3449, 1996a. Wang, Stacy, Miller, Lewis, Gu, Huang, Bushweller, Bories, Alt, Ryan, Liu, Wynshaw-Boris, Binder, Marin-Padilla, Sharpe, Speck, "The Cbf.beta. subunit is essential for CBF.alpha.2 (AML1) function in vivo," Cell, 87:697-708, 1996b. Wang, Wang, Crute, Melnikova, Keller, Speck, "Cloning and characterization of subunits of the T-cell receptor and murine leukemia virus enhancer core-binding factor," Mol. Cell. Biol., 13:3324-3339, 1993. Watson, J. D. et al., Molecular Biology of the Gene, 4th Ed., W. A. Benjamin, Inc., Menlo Park, Calif., 1987. Webb and Hurskainen, J. Biomol. Screen., 1:1 19-121, 1996. Weerasinghe et al., J. Virol., 65:5531-5534, 1991. Weinreb, Shinar, Rodan, "Different pattern of alkaline phosphatase, osteopontin, and osteocalcin expression in developing rat bone visualized by in situ hybridization," J. Bone. Miner. Res., 5:831-842, 1990. Wijmenga, Speck, Dracopoli, Hofker, Liu, Collins, "Identification of a new murine runt domain-containing gene, Cbfa3, and localization of the human homolog, CBFA3, to chromosome 1p35-pter," Genomics, 26:611-614, 1995. Wilkinson, "In situ hybridization," In: In situ hybridization: A practical approach, New York, N.Y.: IRL Press at Oxford University, 11:257-263, 1992. Wolf et al., "An Integrated Family of Amino Acid Sequence Analysis Programs," Compu. Appl. Biosci., 4(1):187-91, 1988. Wong and Neumann, "Electric field mediated gene transfer," Biochim. Biophys. Res. Commun., 107(2):584-587, 1982. Wong et al., "Appearance of .beta.-lactamase activity in animal cells upon liposome mediated gene transfer," Gene, 10:87-94, 1980. Woolf et al., Proc. Natl. Acad. Sci. USA, 89:7305-7309, 1992. Wu and Wu, "Evidence for targeted gene delivery to HepG2 hepatoma cells in vitro," Biochemistry, 27:887-892, 1988. Wu and Wu, "Receptor-mediated in vitro gene transfections by a soluble DNA carrier system," J. Biol. Chem., 262:4429-4432,

1987. Wu and Wu, Adv. Drug Delivery Rev., 12:159-167, 1993. Wu et al., Gene, 190(1):157-162, 1997. Wu, S. J. and Dean, D. H., "Functional significance of loops in the receptor binding domain of Bacillus thuringiensis CryIIIA .delta.-endotoxin," J. Mol. Biol. 255(4):628-640, 1996. Yang et al., "In vivo and in vitro gene transfer to mammalian somatic cells by particle bombardment," Proc. Natl. Acad. Sci. USA, 87:9568-9572, 1990. Yang, Zhang, Davey, Mulligan, Cocking, Plant Cell Rep, 7:421-425, 1988. Young and Davis, "Efficient isolation of genes by using antibody probes," Proc. Natl. Acad. Sci. USA, 80:1194-1198, 1983. Yu et al., Proc. Natl. Acad. Sci. USA, 90:6340-6344, 1993. Zatloukal, Wagner, Cotten, Phillips, Plank, Steinlein, Curiel, Birnstiel, "Transferrinfection: a highly efficient way to express gene constructs in eukaryotic cells," Ann. N.Y. Acad. Sci, 60:136-153, 1992. Zelenin et al., "High-velocity mechanical DNA transfer of the chloramphenicol acetyltransferase gene into rodent liver, kidney and mammary gland cells in organ explants and in vivo," FEBS Lett., 280:94-96, 1991. Zhang et al. "1,25(OH)2 vitamin D.sub.3 inhibits Osteocalcin expression in mouse through an indirect mechanism," J. Biol. Chem., 272:110-116, 1997. Zhou et al., Mol. Cell Biol., 10:4529-4537, 1990.

US-PAT-NO: 6503509

DOCUMENT-IDENTIFIER: US 6503509 B1

TITLE: Method for receptor desensitization

DATE-ISSUED: January 7, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Vilen; Barbara J.	Chapel Hill	NC	N/A	N/A
Cambier; John C.	Denver	CO	N/A	N/A

APPL-NO: 09/ 513024

DATE FILED: February 25, 2000

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application claims priority under 35 U.S.C. .sctn. 119(e) from U.S. Provisional Application Ser. No. 60/121,954, filed Feb. 25, 1999, entitled "Product and Method for Treatment of Conditions Associated with Receptor-Desensitization." The entire disclosure of U.S. Provisional Application Ser. No. 60/121,954 is incorporated herein by reference in its entirety.

US-CL-CURRENT: 424/153.1, 424/130.1 , 424/136.1 , 424/137.1 , 424/141.1 , 424/143.1 , 424/144.1 , 424/152.1 , 424/172.1 , 424/173.1 , 435/70.21 , 514/2 , 514/885 , 530/387.1 , 530/387.3 , 530/388.1 , 530/388.2 , 530/388.22 , 530/388.7 , 530/388.73 , 530/389.1 , 530/389.6

ABSTRACT:

Particular members of the multisubunit immune recognition receptor (MIRR) family of receptors, specifically, the B cell antigen receptor (BCR), the pre-B cell receptor (pre-BCR), the pro-B cell receptor (pro-BCR), Ig Fc receptors (FcR), and NK receptors, can be physically uncoupled from their associated transducers. The invention describes regulatory compounds and methods for mimicking such dissociation/destabilization for the purposes of receptor desensitization and for treatment of conditions in which receptor desensitization or alternatively, enhanced or prolonged receptor sensitization, is desirable. Compounds and methods for enhancing or prolonging receptor sensitization are also disclosed, as are methods for identifying regulatory compounds suitable for use in the present methods.

18 Claims, 15 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 11

---------- KWIC ---------

Detailed Description Text - DETX (76):

Previous studies of desensitized cells suggested that the defect in BCR signaling lies **upstream of src**-family kinase **activation,** possibly at the level of the receptor (Vilen et al., 1997). To address changes in BCR structure under conditions of receptor desensitization, the .mu.-heavy chain, Ig-.alpha. or Ig-.beta. were immunoprecipitated from desensitized K46.mu. cell lysates and the coprecipitated BCR components were quantitatcd. Briefly, a comparative analysis of mIg-Ig-.alpha./Ig-.beta. association in unstimulated K46.mu. cells, cells stimulated 1 hour with NP.sub.7 BSA (500 mg/5.times.10.sup.6 cells/ml) or cells stimulated 1 hour with biotinylated b-7-6 (10 .mu.g/5.times.10.sup.6 /ml) was performed. Biotinylated b-7-6 was prebound to unstimulated cells (10 .mu.g/5.times.10.sup.6 cells/ml) for 2 minutes at 4.degree. C. prior to lysis. FIG. 1 shows the results of the analysis as follows: Panel 1: Lanes 1 and 2 represent IgM and Ig-.alpha. immunoblots of anti-.mu. immunoprecipitates. Panel 2: Lanes 3 and 4 represent IgM, Ig-.beta. and Ig-.alpha. immunoblots of anti-Ig-.beta. immunoprecipitates. Panel 3: Lanes 5 and 6 represent IgM and Ig-.alpha. immunoblots of Ig-.alpha. immunoprecipitates. Panel 4: Lanes 7 and 8 represent IgM and Ig-.alpha. immunoblots of streptavidin immunoprecipitates.

US-PAT-NO: 6495331

DOCUMENT-IDENTIFIER: US 6495331 B1

TITLE: Regulation of cytokine production in a hematopoietic cell

DATE-ISSUED: December 17, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Gelfand; Erwin W.	Englewood	CO	N/A	N/A
Johnson; Gary L.	Boulder	CO	N/A	N/A

APPL-NO: 09/ 305720

DATE FILED: May 5, 1999

PARENT-CASE:

PRIORITY

This application is a continuation of U.S. Ser. No. 08/656,563 filed May 31, 1996, now U.S. Pat. No. 5,910,417, which is hereby incorporated by reference.

US-CL-CURRENT: 435/7.2, 424/85.1 , 435/7.1 , 514/2

ABSTRACT:

A method useful for regulating cytokine production by a hematopoietic cell by regulating an MEKK/JNKK-contingent signal transduction pathway in such a cell is disclosed. Methods of identifying compounds capable of specifically regulating an MEKK/JNKK-contingent signal transduction pathway in hematopoietic cells, a kit for identifying cytokine regulators, methods to treat diseases involving cytokine production, and cells useful in such methods are also set forth.

39 Claims, 28 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 14

---------- KWIC ---------

Detailed Description Text - DETX (32):

The present inventors have unexpectedly found that the PI3-K inhibitor,

wortmannin, at concentrations that inhibit PI3-kinase activity, also inhibited JNK **activation,** but not ERK **activation**. This finding is the first demonstration of a role for PI3-kinase in regulating a JNK pathway by an **Src** family tyrosine kinase-associated receptor. Thus, in mast cells the regulation of the MEKK1, JNKK, JNK pathway is dependent on the **activation** of PI3-kinase, which in turn, is **activated** by aggregation of Fc.epsilon.RI. Mechanistically, there is a very early separation in the signal pathways **activated** by the Fc.epsilon.RI to differentially regulate JNK and ERK sequential protein kinase pathways. Without being bound by theory, the present inventors believe that PI3-kinase activity is involved in **activating** the MEKK/JNKK-contigent pathway in mast cells downstream of tyrosine kinases and **upstream** of MEKK1.

US-PAT-NO: 6492124

DOCUMENT-IDENTIFIER: US 6492124 B1

TITLE: Trance activated signal transduction pathways in osteoclasts

DATE-ISSUED: December 10, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Wong; Brian	New York	NY	N/A	N/A
Besser; Daniel	New York	NY	N/A	N/A
Choi; Yongwon	New York	NY	N/A	N/A

APPL-NO: 09/ 330867

DATE FILED: June 11, 1999

US-CL-CURRENT: 435/7.1, 514/2 , 530/350

ABSTRACT:

The present invention relates to methods and compositions for modulating activity of a TRANCE receptor, including the modulation of TRANCE signaling activity. In particular, the invention provides screening methods by which novel modulators of TRANCE signaling may be identified, including TRANCE inhibitors, agonists and antagonists. The invention also relates to the identification of one or more specific pathways for osteoclast surivival, and the manipulation of this pathway (e.g., using a TRANCE modulator of the invention). Such manipulation may provide strategies for treating osteoclast-related diseases such as osteoporosis and osteopetrosis.

39 Claims, 19 Drawing figures

Exemplary Claim Number: 1,17

Number of Drawing Sheets: 8

---------- KWIC ---------

Detailed Description Text - DETX (69):

Alternatively, inhibition of **upstream** signal transduction mechanisms can block AKT **activation**. For example, inhibition of **Src**, Cbl, or PIK3 **activation** may block AKT **activation**. Such inhibitors include various kinase inhibitors. Preferably, such inhibitors are specific for the signal transduction factors in the AKT **activation** pathway.

Detailed Description Text - DETX (110):

Several cytokines that modulate immune responses **activate Src**-family kinases through unknown mechanisms. For example, CD40L can **activate** Lyn in Daudi B-cells and LPS can stimulate Lyn, Fgr and Hck in monocytes. Our results demonstrating that TRAF6 can associate with c-**Src** or Fyn in co-expression assays and/or primary cells implicate TRAF6 in the regulation of **Src**-family kinases by several types of signaling receptors that engage TRAF6. TRAF1 and TRAF3also associated with c-**Src** providing evidence that these adapter molecules function by recruiting **Src**-family kinases to their **upstream** receptors. It will be interesting to determine the relevance of the association of TRAF1 and TRAF3with c-**Src or Src**-family kinases in vivo. Taken together, TRAF6 and possibly TRAF1 and TRAF3 may bridge a variety of cytokine receptors to specific **Src**-family kinases.

US-PAT-NO: 6475778

DOCUMENT-IDENTIFIER: US 6475778 B1

TITLE: Differentiation enhancing factors and uses therefor

DATE-ISSUED: November 5, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Roberts; Thomas M.	Cambridge	MA	N/A	N/A
King; Frederick J.	Brookline	MA	N/A	N/A
Harris; David F.	Gales Ferry	CT	N/A	N/A
Hu; Erding	King of Prussia	PA	N/A	N/A
Spiegelman; Bruce	Waban	MA	N/A	N/A
Chan; Joanne	Brookline	MA	N/A	N/A

APPL-NO: 09/ 023905

DATE FILED: February 13, 1998

PARENT-CASE:

RELATED APPLICATIONS

This application claims priority to U.S. Provisional Application No. 60/038,191 filed on Feb. 14, 1997, the contents of which are incorporated herein by reference.

US-CL-CURRENT: 435/320.1, 435/325 , 435/455 , 435/69.1 , 536/23.1 , 536/23.5

ABSTRACT:

The present invention relates to novel SH3 domain binding protein, referred to herein a DEF polypeptides. The DEF polypeptides comprise several motifs including a src SH3 consensus binding sequence, four ankyrin repeats, one zinc finger domain and six copies of a proline-rich tandem repeat. DEF polypeptides may function as mediators of SH3 domain-dependent signal transduction pathways and, thus may mediate multiple signaling events such as cellular gene expression, cytoskeletal architecture, protein trafficking and endocytosis, cell adhesion, migration, proliferation and differentiation. Described herein are isolated and antisense nucleic acids molecules, recombinant expression vectors, host cells and non-human transgenic animals containing an insertion or a disruption of the DEF gene. Diagnostic, screening and therapeutic methods utilizing the compositions of the invention are also provided

12 Claims, 37 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 34

---------- KWIC ---------

Detailed Description Text - DETX (129):

The invention also provides for reduction of the mammalian DEF proteins to generate mimetics, e.g. peptide or non-peptide agents, which are able to disrupt binding of a mammalian DEF polypeptide of the present invention with binding proteins or interactors. Thus, such mutagenic techniques as described above are also useful to map the determinants of the DEF proteins which participate in protein-protein interactions involved in, for example, binding of the subject mammalian DEF polypeptide to proteins which may function **upstream** (including both **activators** and repressors of its activity) or to proteins or nucleic acids which may function downstream of the DEF polypeptide, whether they are positively or negatively regulated by it. To illustrate, the critical residues of a subject DEF polypeptide which are involved in molecular recognition of interactor proteins or molecules **upstream** or downstream of a DEF (such as, for example, a **src** SH3 binding site, a zinc finger domain, an ankyrin repeat) can be determined and used to generate DEF-derived peptidomimetics which competitively inhibit binding of the authentic DEF protein to that moiety. By employing, for example, scanning mutagenesis to map the amino acid residues of each of the subject DEF proteins which are involved in binding other intracellular proteins, peptidomimetic compounds can be generated which mimic those residues of the DEF protein which facilitate the interaction. Such mimetics may then be used to interfere with the normal function of a DEF protein. For instance, non-hydrolyzable peptide analogs of such residues can be generated using benzodiazepine (e.g., see Freidinger et al. in Peptides: Chemistry and Biology, G. R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), azepine (e.g., see Huffman et al. in Peptides: Chemistry and Biology, G. R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), substituted .gamma. lactam rings (Garvey et al. in Peptides: Chemistry and Biology, G. R. Marshall ed., ESCOM Publisher: Leiden, Netherlands, 1988), keto-methylene pseudopeptides (Ewenson et al. (1986) J Med Chem 29:295; and Ewenson et al. in Peptides: Structure and Function (Proceedings of the 9th American Peptide Symposium) Pierce Chemical Co. Rockland, Ill., 1985), b-turn dipeptide cores (Nagai et al. (1985) Tetrahedron Lett 26:647; and Sato et al. (1986) J Chem Soc Perkin Trans 1:1231), and b-aminoalcohols (Gordon et al. (1985) Biochem Biophys Res Commun 126:419; and Dann et al. (1986) Biochem Biophys Res Commun 134:71).

US-PAT-NO: 6472520

DOCUMENT-IDENTIFIER: US 6472520 B2

TITLE: Rat PEG-3 promoter

DATE-ISSUED: October 29, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Fisher; Paul B.	Scarsdale	NY	N/A	N/A

APPL-NO: 09/ 052753

DATE FILED: March 31, 1998

PARENT-CASE:

This application is a continuation-in-part of International Application No. PCT/US98/05783, filed Mar. 20, 1998, which is a continuation-in-part of U.S. application Ser. No. 08/821,818, filed Mar. 21, 1997 now U.S. Pat. No. 6,146,877. The content of both International Application No. PCT/US98/05783 and U.S. application Ser. No. 08/821,818 is hereby incorporated into this application by reference.

US-CL-CURRENT: 536/24.1, 435/320.1 , 536/23.1

ABSTRACT:

This invention provides a vector suitable for introduction into a cell, having: a) an inducible PEG-3 regulatory region; and b) a gene encoding a product that causes or may be induced to cause the death or inhibition of cancer cell growth. In addition, this invention further provides the above-described vectors, wherein the inducible PEG-3 regulatory region is a promoter. This invention further provides the above-described vectors, wherein the gene encodes an inducer of apoptosis. In addition, this invention provides the above-described vectors, wherein the gene is a tumor suppressor gene. In addition, this invention provides the above-described vectors, wherein the gene encodes a viral replication protein. This invention also provides the above-described vectors, wherein the gene encodes a product toxic to cells or an intermediate to a product toxic to cells. In addition, this invention provides the above-described vectors, wherein the gene encodes a product causing enhanced immune recognition of the cell. This invention further provides the above-described vectors, wherein the gene encodes a product causing the cell to express a specific antigen.

10 Claims, 39 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 39

---------- KWIC ---------

Detailed Description Text - DETX (428):

Nuclear run-on assays indicate that PEG-3 expression directly correlates with an increase in the rate of RNA transcription (17). This association is supported by the isolation of a genomic fragment **upstream** of the 5' untranslated region of the PEG-3 cDNA and demonstration that this sequence linked to a luciferase reporter gene is **activated** as a function of cancer progression, oncogenic transformation and DNA damage (FIGS. 15, 16 & 17). Additionally, changes in the stability of PEG-3 mRNA may also contribute to differential expression of this gene as a function of cancer progression, oncogene expression and DNA damage. To address this issue mRNA stability (RNA degradation) assays will be performed as described in detail previously (43). Our analysis focuses on the effect of cancer progression (E11-NMT, R1 and R2 cells), oncogenic transformation (Ha-ras, V**-src,** H5hr1 and HPV-18 transformed CREF cells) and DNA damage (gamma irradiation and MMS-treatment of CREF cells). Appropriate controls, E11, untransformed CREF cells and CREF cells not treated with DNA damaging agents, respectively, and experimental samples will be incubated without additions or in the presence of 5 mg/ml of actinomycin D (in the dark), and 30, 60 and 120 min later, total cellular RNA will be isolated and analyzed for gene expression using Northern hybridization. RNA blots will be quantitated by densitometric analysis using a Molecular Dynamics densitometer (Sunnyvale, Calif.). These straight forward experiments will indicate if the stability of PEG-3 is altered in cells as a direct consequence of spontaneous progression, expression of defined oncogenes or as a consequence of DNA damage.

Detailed Description Text - DETX (473):

Nuclear run-on assays indicate that PEG-3 expression directly correlates with an increase in the rate of RNA transcription (17). This association is supported by the isolation of a genomic fragment **upstream** of the 5' untranslated region of the PEG-3 cDNA and demonstration that this sequence linked to a luciferase reporter gene is **activated** as a function of cancer progression, oncogenic transformation and DNA damage. Additionally, changes in the stability of PEG-3 mRNA may also contribute to differential expression of this gene as a function of cancer progression, oncogene expression and DNA damage. To address this issue mRNA stability (RNA degradation) assays will be performed as described in detail previously (32). Our analysis will focus on the effect of cancer progression (E11-NMT, R1 and R2 cells), oncogenic transformation (Ha-ras, V**-src,** H5hr1 and HPV-18 transformed CREF cells) and DNA damage (gamma irradiation and MMS-treatment of CREF cells). Appropriate controls, E11, untransformed CREF cells and CREF cells not treated with DNA damaging agents, respectively, and experimental samples will be incubated without additions or in the presence of 5 .mu.g/ml of actinomycin D (in the dark), and 30, 60 and 120 min later, total cellular RNA will be isolated and analyzed for gene expression using Northern hybridization. RNA blots will be quantitated by densitometric analysis using a Molecular Dynamics densitometer (Sunnyvale, Calif.) (32). These straight forward experiments will indicate if

the stability of PEG-3 is altered in cells as a direct consequence of spontaneous progression, expression of defined oncogenes or as a consequence of DNA damage.

US-PAT-NO: 6472197

DOCUMENT-IDENTIFIER: US 6472197 B1

TITLE: GRB2 associating polypeptides and nucleic acids encoding therefor

DATE-ISSUED: October 29, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Pot; David A.	San Francisco	CA	N/A	N/A
Williams; Lewis T.	Tiburon	CA	N/A	N/A
Jefferson; Anne Bennett	University City	MO	N/A	N/A
Majerus; Philip W.	University City	MO	N/A	N/A

APPL-NO: 09/ 969528

DATE FILED: October 1, 2001

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is a divisional of, and claims the benefit of priority from, U.S. patent application Ser. No. 09/418,540, filed Oct. 14, 1999, now U.S. Pat. No. 6,296,848, which is a continuation of U.S. application Ser. No. 08/560,005, filed Nov. 17, 1995, now U.S. Pat. No. 6,001,354, the full disclosures of which are incorporated herein by reference in their entirety.

The present invention generally relates to novel GRB2 associating polypeptides and nucleic acids which encode these polypeptides. In particular, these novel polypeptides possess inositol polyphosphate 5-phosphatase activity, important in growth factor mediated signal transduction. As such, the polypeptides, nucleic acids encoding the polypeptides, cells capable of expressing these nucleic acids and antibodies specific for the polypeptides will find a variety of uses in a wide range of screening, therapeutic and other applications.

US-CL-CURRENT: 435/252.3, 435/194 , 435/320.1 , 530/300 , 530/350 , 536/23.2

ABSTRACT:

The present invention generally relates to novel GRB2 associating proteins and nucleic acids which encode these protein. In particular, these novel proteins possess inositol polyphosphate 5-phosphatase and phosphatidylinositol 5-phosphatase activities, important in growth factor mediated signal transduction. As such, the proteins, nucleic acids encoding the proteins, cells capable of expressing these nucleic acids and antibodies specific for these proteins will find a variety of uses in a variety of screening,

therapeutic and other applications.

6 Claims, 30 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 27

---------- KWIC ---------

Detailed Description Text - DETX (7):

PtdIns(3,4,5)P.sub.3 in particular, is the product of phosphatidyl inositol 3-kinase ("PI3 kinase"), an important agonist **activated** signaling protein, stimulated in growth factor mediated signal transduction. PI3-kinase is known to be involved in the regulation of cell growth and oncogenic transformation (Cantley et al., Cell, 64:1657 (1993)). Upon growth factor receptor stimulation, the wild-type PI3-kinase is **activated** and can phosphorylate phosphatidylinositol ("PtdIns") at the 3' position of the inositol ring. These phosphatidylinositol 3-phosphates are candidate second messenger molecules. The PI3-kinase enzyme is found associated with receptor protein tyrosine kinases such as PDGF-R-.beta., CSF-1 receptor, Insulin receptor and IGF-1 receptor as well as non-receptor tyrosine kinase oncogenes, e.g., **src,** gag-abl and fyn. Studies on mutants of platelet-derived growth factor (PDGF) receptor have shown that PI3-kinase is a key mediator of PDGF-mediated mitogenic signaling (Fantl et al., Cell, 69:413 (1992); Valius et al., ibid., 73:321 (1993)). PDGF-R mutants that are unable to bind PI3-kinase are also unable to induce a mitogenic response after growth factor stimulation and unable to **activate** p21c-Ras (Ras). These data indicate that PI3-kinase acts **upstream** of Ras in PDGF-stimulated signaling. Studies also indicate that the PI3-kinase product, PtdIns(3,4,5)P.sub.3 is not the final product produced during the initial phases of signaling, indicating further processing of this signaling molecule. Stephens, et al., Nature 351:33-39 (1991), Hawkins, et al., Nature 358:157-159 (1992).

US-PAT-NO: 6469063

DOCUMENT-IDENTIFIER: US 6469063 B1

TITLE: Inhibition of inflammation via inhibition of COX-2 gene transcription

DATE-ISSUED: October 22, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Bleich; David	Pasadena	CA	N/A	N/A
Chen; Songyuan	Duarte	CA	N/A	N/A
Han; Xiao	Duarte	CA	N/A	N/A

APPL-NO: 09/ 714889

DATE FILED: November 17, 2000

PARENT-CASE:

CROSS-REFERENCE TO RELATED APPLICATIONS

This application is related to provisional application No.60/166,161, filed Nov. 18, 1999, the specification of which is incorporated herein by reference.

US-CL-CURRENT: 514/538, 514/540

ABSTRACT:

The present invention is directed to a method of treating inflammation comprising administering to a subject in need thereof an amount of a caffeic acid derivative sufficient to inhibit the transcription of COX-2. In a preferred embodiment the caffeic acid derivative is a cyanocinnamate, most preferably cinnamamyl-3,4-dihydroxy-.alpha.-cyanocinnamate.

5 Claims, 9 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 9

---------- KWIC ---------

Detailed Description Text - DETX (2):

It has previously been published that 12-HETE, the major 12-LO end product, induces JNK in RIN m5F cells [28]. Furthermore, Herschmann and colleagues demonstrated that v-**src** induces COX-2 gene transcription by **activating** JNK and

c-jun [29]. These studies demonstrate that c-jun may **activate** COX-2 gene transcription by binding to the cAMP response element (CRE) in the COX-2 promoter. In the present study it is demonstrated that 12-HETE acts as a specific **upstream** agent in **activating** COX-2 gene transcription. As seen in FIG. 9, a schematic signaling pathway is depicted that identifies key elements in the pathway leading from cytokine-stimulation to COX-2 gene **activation** in pancreatic .beta.-cells. Furthermore, since rat tissue does not contain the putative CRE in the COX-2 promoter, it is likely that 12-HETE regulates COX-2 gene transcription through a novel promoter sequence.

	L #	Hits	Search Text	DBs	Time Stamp
1	L1	116	hbx	USPAT; US-PGPUB	2003/07/08 09:44
2	L2	362	(hepatitis adj b adj virus or hbv) near4 inhibit$8	USPAT; US-PGPUB	2003/07/08 09:45
3	L3	15	1 and 2	USPAT; US-PGPUB	2003/07/08 09:45
4	L4	6	hbx near4 inhibit$8	USPAT; US-PGPUB	2003/07/08 10:44
5	L5	7091	src	USPAT; US-PGPUB	2003/07/08 10:46
6	L6	665867	activat$8	USPAT; US-PGPUB	2003/07/08 10:46
7	L7	201531	upstream	USPAT; US-PGPUB	2003/07/08 10:47
8	L8	2769	6 near5 7	USPAT; US-PGPUB	2003/07/08 10:47
9	L9	19	8 same 5	USPAT; US-PGPUB	2003/07/08 10:47
10	L10	61	5 same 6 same 7	USPAT; US-PGPUB	2003/07/08 10:53
11	L11	221	5 near2 (activator$1 or activation)	USPAT; US-PGPUB	2003/07/08 11:17
12	L12	2937	hbv or hbx	USPAT; US-PGPUB	2003/07/08 11:17
13	L13	9	11 and 12	USPAT; US-PGPUB	2003/07/08 11:18

PGPUB-DOCUMENT-NUMBER: 20030096816

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030096816 A1

TITLE: Inhibitors of c-Jun N-terminal kinases (JNK) and other protein kinases

PUBLICATION-DATE: May 22, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Cao, Jingrong	Newton	MA	US	
Green, Jeremy	Burlington	MA	US	
Moon, Young-Choon	Lexington	MA	US	
Wang, Jian	Boston	MA	US	
Ledeboer, Mark	Acton	MA	US	
Harrington, Edmund	South Boston	MA	US	
Gao, Huai	Natick	MA	US	

APPL-NO: 10/ 121035

DATE FILED: April 10, 2002

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60283621 20010413 US

non-provisional-of-provisional 60329440 20011015 US

non-provisional-of-provisional 60292974 20010523 US

US-CL-CURRENT: 514/242, 514/252.01 , 514/275 , 544/182 , 544/238 , 544/331

ABSTRACT:

The present invention provides compounds of formula I: 1 or a pharmaceutically acceptable derivative o thereof, wherein A, B, R.sup.a, R.sup.1, R.sup.2, R.sup.3, and R.sup.4 are as described in the specification. These compounds are inhibitors of protein kinase, particularly inhibitors of JNK, a mammalian protein kinase involved cell proliferation, cell death and response to extracellular stimuli; Lck and Src kinase. The invention also relates to methods for producing these inhibitors. The invention also provides pharmaceutical compositions comprising the inhibitors of the invention and methods of utilizing those compositions in the treatment and prevention of various disorders.

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit of priority to co-pending U.S.

provisional applications 60/283,621 filed Apr. 13, 2001, 60/329,440 filed Oct. 14, 2001 and 60/292,974 filed May 23, 2001.

---------- KWIC ---------

Summary of Invention Paragraph - BSTX (19):
[0018] Src also plays a role in the replication of hepatitis B virus. The virally encoded transcription factor **HBx** activates Src in a step required for propagation of the virus. Klein et al., EMBO J., 18, 5019, (1999) and Klein et al., Mol.Cell. Biol., 17, 6427 (1997).

Summary of Invention Paragraph - BSTX (22):
[0021] Accordingly, there is still a great need to develop potent inhibitors of JNKs and Src family kinases that are useful in treating various conditions associated with JNK and **Src activation**.

PGPUB-DOCUMENT-NUMBER: 20030032596

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030032596 A1

TITLE: Inhibition of the Src kinase family pathway as a method of treating **HBV** infection and hepatocellular carcinoma

PUBLICATION-DATE: February 13, 2003

US-CL-CURRENT: 514/12, 514/262.1 , 514/44

APPL-NO: 10/ 196344

DATE FILED: July 15, 2002

RELATED-US-APPL-DATA:

child 10196344 A1 20020715

parent continuation-of 08874430 19970613 US GRANTED

parent-patent 6420338 US

PGPUB-DOCUMENT-NUMBER: 20030022196

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030022196 A1

TITLE: Methods and compositions for screening for altered cellular phenotypes

PUBLICATION-DATE: January 30, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Lorens, James	Portola Valley	CA	US	
Kinsella, Todd M.	Fayetteville	CA	US	
Masuda, Esteban	Menlo Park	CA	US	
Hitoshi, Yasumichi	Mountain view	CA	US	
Liao, X. Charlene	Palo Alto	CA	US	
Pearsall, Denise	Belmont	CA	US	
Friera, Annabelle	South San Francisco	CA	US	
Chu, Peter	San Francisco	CA	US	

APPL-NO: 10/ 096339

DATE FILED: March 8, 2002

RELATED-US-APPL-DATA:

child 10096339 A1 20020308

parent continuation-in-part-of 09076624 19980512 US PENDING

US-CL-CURRENT: 435/6, 435/325 , 435/455 , 435/7.21

ABSTRACT:

The invention relates to methods and compositions useful for screening for altered cellular phenotypes using an inducible expression system to enrich for and detect the altered phenotypes and, more particularly, relates to screening libraries of candidate bioactive agents, for example, nucleic acids and peptides, in cells using an regulatable expression system to enrich for a subpopulation of cells having an altered phenotype due to the presence of a candidate bioactive agent.

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 09/076,624, filed May 12, 1998 (pending).

---------- KWIC ---------

Detail Description Paragraph - DETX (209):

[0274] In a preferred embodiment, the present methods are useful in infectious disease applications. Viral latency (herpes viruses such as CMV, EBV, **HBV,** and other viruses such as HIV) and their reactivation are a significant problem, particularly in immunosuppressed patients (patients with AIDS and transplant patients). The ability to block the reactivation and spread of these viruses is an important goal. Cell lines known to harbor or be susceptible to latent viral infection can be infected with the specific virus, and then stimuli applied to these cells which have been shown to lead to reactivation and viral replication. This can be followed by measuring viral titers in the medium and scoring cells for phenotypic changes. Candidate libraries can then be inserted into these cells under the above conditions, and peptides isolated which block or diminish the growth and/or release of the virus. As with chemotherapeutics, these experiments can also be done with drugs which are only partially effective towards this outcome, and bioactive agents isolated which enhance the virucidal effect of these drugs.

Detail Description Paragraph - DETX (282):

[0337] Activation of specific signaling pathways in lymphocytes determines the quality, magnitude and duration of immune responses. In transplantation, acute and chronic inflammatory diseases, and autoimmunity, it is these pathways that are responsible for the induction, maintenance and exacerbation of disease lymphocyte responses. In all cases, recognition of antigens presented by the Major Histocompatability Complex (MHC) by the T cell receptor (TCR) complex triggers the activation of T lymphocytes. Engagement of the TCR by antigen/MHC results in actin cytoskeleton rearrangement, induction of cyrokine and other gene transcription, and progression into the cell cycle.sup.1,2. The proximal events of TCR signaling include **activation of src** family kinases LCK, FYN, phosphorylation of TCR component (.) and subsequent activation of ZAP70/SYK tyrosine kinases, as well as recruitmentof adaptormolecules(CBL-B, LAT, SLP76), which couple to more distal signaling pathways including Ras and PLC(.sup.3-5. New components of the TCR signaling pathway have been discovered and reported, such as the new transmembrane adaptor PAG/CBP.sup.6, albeit with a slower pace. It has become apparent that identifying additional signaling molecules requires novel approaches including functional genomics. Using the methods of the present invention, novel signaling molecules specific for T cell activation and effector function were identified and validated.

US-PAT-NO: 6503914

DOCUMENT-IDENTIFIER: US 6503914 B1
See image for Certificate of Correction

TITLE: Thienopyrimidine-based inhibitors of the Src family

DATE-ISSUED: January 7, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Benish; Michele A.	Pearland	TX	N/A	N/A
Lawless; Michael	St. Charles	MO	N/A	N/A
Budde; Raymond J. A.	Bellaire	TX	N/A	N/A

APPL-NO: 09/ 694145

DATE FILED: October 23, 2000

US-CL-CURRENT: 514/260.1, 544/278

ABSTRACT:

Various thienopyrimidine-based analog compounds that selectively inhibit the Src family of tyrosine kinases. These compounds are thienopyrimidines and contain a hydrozone bridge created by heating a thienopyrimidine hydrazine with an aldehyde in ethanol at reflux. Such compounds are useful in the treatment of various diseases including hyperproliferative diseases, hematologic diseases, osteoporosis, neurological diseases, autoimmune diseases, allergic/immunological diseases, or viral infections.

99 Claims, 6 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

---------- KWIC ---------

Brief Summary Text - BSTX (12):

Herpesviridae, papovaviridae, and retroviridae have been shown to interact with non-receptor tyrosine kinases and use them as signaling intermediates. The HIV-1 Nef protein interacts with members of the Src family of tyrosine kinases. Nef mediates downregulation of CD4 membrane expression, modification of T-cell activation pathways, and increases virus infectivity (Collette et al., 1997). The **HBx** protein of the hepatitis B virus is essential for infection by hepadnaviruses and activates Ras by activating the Src family of tyrosine kinases. The activation of Ras is necessary for the ability of the

HBx protein to stimulate transcription and release growth arrest in quiescent cells (Klein and Schneider, 1997). Activity of the Src family of tyrosine kinases is altered by association with viral proteins such as mouse and hamster polyomavirus middle-T antigens, Epstein-Barr virus LMP2A, and herpesvirus saimiri Tip (Dunant and Ballmer-Hofer, 1997).

Detailed Description Text - DETX (205):
Bolen J B, Veillette A, Schwartz A M, Deseau V, Rosen N**: Activation of pp60c-src** in human colon carcinoma and normal human colon mucosal cells. Oncogene Res 1:149-168, 1987.

Detailed Description Text - DETX (206):
Bolen J B, Veillette A, Schwartz A M, Deseau V, Rosen N**: Activation of pp60c-src** protein kinase activity in human colon carcinoma. Proc Natl Acad Sci USA 84:2251-2255, 1987.

Detailed Description Text - DETX (216):
Cartwright C A, Kamps M P, Meisler A I, Pipas J M, Eckhart W: p60c**-src activation** in human colon carcinoma. J Clin Invest 83:2025-2033, 1989.

Detailed Description Text - DETX (217):
Cartwright C A, Meisler A I, Eckhart W**: Activation of the pp60c-src** protein kinase is an early event in colonic carcinogenesis. Proc Natl Acad Sci USA 87:558-562, 1990.

Detailed Description Text - DETX (219):
Chackalaparampil I, Shalloway D: Altered phosphorylation and **activation of pp60c-src** during fibroblast mitosis. Cell 52:801-810, 1988.

Detailed Description Text - DETX (255):
Klein N P and Schneider R J. **Activation of Src** Family Kinases by Hepatitis B Virus **HBx** Protein and Coupled Signaling to Ras. Mol Cell Biol 17:6427-6436, 1997.

Detailed Description Text - DETX (281):
Sabe H, Okada M, Nakagawa H, Hanafusa H**: Activation of c-src** in cells bearing v-Crk and its suppression by C S K. Mol. Cell Biol. 12:4706-4713, 1992.

Detailed Description Text - DETX (313):
Zheng X M, Wang Y, and Pallen C J: Cell transformation and **activation of pp60c-src** by overexpression of a protein tyrosine phosphatase. Nature 359:336-339, 1992.

	L #	Hits	Search Text	DBs	Time Stamp
1	L1	116	hbx	USPAT; US-PGPUB	2003/07/08 09:44
2	L2	362	(hepatitis adj b adj virus or hbv) near4 inhibit$8	USPAT; US-PGPUB	2003/07/08 09:45
3	L3	15	1 and 2	USPAT; US-PGPUB	2003/07/08 09:45
4	L4	6	hbx near4 inhibit$8	USPAT; US-PGPUB	2003/07/08 10:44
5	L5	7091	src	USPAT; US-PGPUB	2003/07/08 10:46
6	L6	665867	activat$8	USPAT; US-PGPUB	2003/07/08 10:46
7	L7	201531	upstream	USPAT; US-PGPUB	2003/07/08 10:47
8	L8	2769	6 near5 7	USPAT; US-PGPUB	2003/07/08 10:47
9	L9	19	8 same 5	USPAT; US-PGPUB	2003/07/08 10:47
10	L10	61	5 same 6 same 7	USPAT; US-PGPUB	2003/07/08 10:53
11	L11	221	5 near2 (activator$1 or activation)	USPAT; US-PGPUB	2003/07/08 11:17
12	L12	2937	hbv or hbx	USPAT; US-PGPUB	2003/07/08 11:17
13	L13	9	11 and 12	USPAT; US-PGPUB	2003/07/08 11:18
14	L14	529	5 near5 6	USPAT; US-PGPUB	2003/07/08 11:38
15	L15	29	12 and 14	USPAT; US-PGPUB	2003/07/08 11:38

PGPUB-DOCUMENT-NUMBER: 20030104975

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030104975 A1

TITLE: Cofactor-based screening method for nuclear receptor modulators and related modulators

PUBLICATION-DATE: June 5, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Auwerx, Johan	Hindisheim		FR	
Chambon, Pierre	Blaesheim		FR	
Picard, Frederic	Strasbourg		FR	

APPL-NO: 10/ 170682

DATE FILED: June 14, 2002

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60297772 20010614 US

US-CL-CURRENT: 514/1, 435/6 , 435/7.1

ABSTRACT:

The invention relates to methods that enable identification of modulators of nuclear receptor (NR) activity and to methods for treating and/or preventing diseases or pathologic conditions associated with cell types that express said nuclear receptors. More particularly, the invention concerns to methods enabling the identification of compounds that induce or inhibit the recruitment of the p160 family cofactors, especially TIF-2 and/or SRCs cofactors and that are useful for modulating the PPAR-gamma biological activity and for treating and/or preventing various PPAR-gamma related diseases and conditions, including metabolic or cell proliferative disorders.

CROSS-REFERENCE TO PROVISIONAL APPLICATION

[0001] This application claims priority under 35 U.S.C. .sctn.119 to U.S. Provisional Application No. 60/297,772, entitled COFACTOR-BASED SCREENING METHOD FOR PPAR GAMMA MODULATORS, filed Jun. 14, 2001, the entire content of which is hereby incorporated by reference.

---------- KWIC ---------

Summary of Invention Paragraph - BSTX (182):

[0183] Other examples of disease or pathologic condition according to the invention are chronic viral infections (e.g. HIV, CMV, HSV, **HBV,** HCV infections), neurodegenerative diseases (e.g. Alzheimer's disease, multiple sclerosis, Parkinson's disease), cardiovascular disease (e.g. atherosclerosis, atherogenesis, vascular restenosis, congestive heart failure), diseases or conditions involving hypoxemia and hypoxic stress (stroke, vascular occlusive disease, MI, atherosclerosis, retinitis, retinal vein occlusion, hypoxic retinopathy, macular degeneration).

Summary of Invention Paragraph - BSTX (202):

[0203] The present invention further concerns special uses of cells and tissues from the above transgenic mammals in which the gene encoding the cofactor has been disrupted. Preferably, said cells and tissues are selected from the group consisting in adipocytes, hepatocytes, skeletal muscle cells, pancreatic beta cells, and related tissues. In preferred embodiment, said cells and tissues are derived from TIF2 -/- or from SRC-1 -/- null mice using standard methods of the art. More specifically, said cells and tissues are used to identify compounds that **activate transcription through a PPAR-gamma/SRC** pathway rather than through a PPAR-gamma/TIF2 pathway (or vice-versa).

Summary of Invention Paragraph - BSTX (203):

[0204] Thus, the present invention further concerns a method of screening for compounds that **activate transcription through a PPAR-gamma/SRC** pathway rather than through a PPAR-gamma/TIF2 pathway, the method comprising:

PGPUB-DOCUMENT-NUMBER: 20030104358

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030104358 A1

TITLE: Diagnosis methods based on microcompetition for a limiting GABP complex

PUBLICATION-DATE: June 5, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Polansky, Hanan	Rochester	NY	US	

APPL-NO: 10/ 219649

DATE FILED: August 15, 2002

RELATED-US-APPL-DATA:

child 10219649 A1 20020815

parent continuation-in-part-of 09732360 20001207 US PENDING

US-CL-CURRENT: 435/5, 435/6

ABSTRACT:

Microcompetition for GABP between a foreign polynucleotide and cellular GABP regulated genes is a risk factor associated with many chronic diseases such as obesity, cancer, atherosclerosis, stroke, osteoarthritis, diabetes, asthma, and other autoimmune diseases. The invention uses this novel discovery to present assays for the diagnosis of these chronic diseases. The assays are based on measuring the cellular copy number of the foreign polynucleotide, measuring the rate of complex formation between GABP and either the foreign polynucleotide, or a cellular GABP regulated gene, identifying modified expression of a cellular GABP regulated gene, or identifying modified activity of the gene product of a GABP regulated gene. The invention also presents other foreign polynucleotide-type assays.

---------- KWIC ---------

Detail Description Paragraph - DETX (322):

[0352] Another p300/cbp factor is NF-Y (see above). Mantovani 1998 (ibid) provides a list of viruses which include a NF-Y binding site (Table 1). The list includes **HBV** S, MSV LTR, RSV LTR, ad EIIL II, Ad MK, CMV gpUL4, HSV IE110k, VZV ORF62, MVM P4.

Detail Description Paragraph - DETX (1537):

[1555] The fourth point requires an understanding of the "mechanisms of virus mediated cell transformation." Crawford (1986.sup.435) and Butel (2000, ibid) also emphasize the significance of understanding the mechanism in attributing a causal role to infection. According to Crawford: "one alternative approach to understanding the role of the papillomaviruses in cervical carcinoma is to identify the mechanisms by which this group of viruses may induce the malignant transformation of normal cells." According to Butel: "molecular studies detected viral markers in tumors, but the mechanism of **HBV** involvement in liver carcinogenesis remains the subject of investigation today." When the other kind of evidence is in place, understanding the mechanism turns a mere association into a causal relation.

Detail Description Table CWU - DETL (7):

5 Virus Cancer Epstein-Bar virus (EBV) Burkitt's lymphoma (BL) Nasopharyngeal carcinoma (NPC) Hodgkin's disease Some T-cell lyphomas Polymorphic B cell lymphomas B-cell lymphoproliferation in immunosuppressed individuals Breast cancer SV40 Brain tumors Osteosacromas Mesotheliomas HIV Breast cancer Human T cell lymphotrophic Adult T-cell leukemia virus-I (HTLV-I) Human papilloma virus Anogenital cancers (HPV) Skin cancers Oral cancers Hepatitis B virus (**HBV**) Hepatocellular carcinoma Hepatitis C virus (HCV) Hepatocellular carcinoma Human herpes virus 8 Kaposi's sarcoma (HHV8, KSHV) Body cavity lymphoma

Detail Description Table CWU - DETL (24):

patterns: the American paradox. Am J Med. 1997 Mar; 102(3): 259-64. .sup.463 Hebebrand J, Wulftange H, Goerg T, Ziegler A, Hinney A, Barth N, Mayer H, Remschmidt H. Epidemic obesity: are genetic factors involved via increased rates of assortative mating? Int J Obes Relat Metab Disord. 2000 Mar; 24(3): 345-53. .sup.464 Hill J O, Peters J C. Environmental contributions to the obesity epidemic. Science. 1998 May 29; 280(5368): 1371-4. .sup.465 Koplan J P, Dietz W H. Caloric imbalance and public health policy. JAMA. 1999 Oct 27; 282(16): 1579-81. .sup.466 Beattie J H, Wood A M, Newman A M, Bremner I, Choo K H A, Michalska A E, Duncan J S, Trayhurn P. Obesity and hyperleptinemia in metallothionein (-I and -II) null mice. Proc. Natl. Acad. Sci. USA 1998 95(1): 358-363. .sup.467 Dong Z M, Gutierrez-Ramos J C, Coxon A, Mayadas T N, Wagner D D. A new class of obesity genes encodes leukocyte adhesion receptors. Proc. Natl. Acad. Sci. USA 1997 (94): 7526-7530. .sup.468 Large V, Reynisdottir S, Langin D, Fredby K, Klannemark M, Holm C, Arner P. Decreased expression and function of adipocyte hormone-sensitive lipase in subcutaneous fat cells of obese subjects. J Lipid Res. 1999 Nov; 40(11): 2059-66. .sup.469 Elizalde M, Ryden M, van Harmelen V, Eneroth P, Gyllenhammar H, Holm C, Ramel S, Olund A, Arner P, Andersson K. Expression of nitric oxide synthases in subcutaneous adipose tissue of nonobese and obese humans. J Lipid Res. 2000 Aug; 41(8): 1244-51. .sup.470 Maudsley S, Pierce K L, Zamah A M, Miller W E, Ahn S, Daaka Y, Lefkowitz R J, Luttrell L M. The beta(2)-adrenergic receptor mediates extracellular signal-regulated kinase activation via assembly of a multi-receptor complex with the epidermal growth factor receptor. J Biol Chem. 2000 Mar 31; 275(13): 9572-80. .sup.471 Pierce K L, Maudsley S, Daaka Y, Luttrell L M, Lefkowitz R J. Role of endocytosis in

the activation of the extracellular signal-regulated kinase cascade by sequestering and nonsequestering G protein-coupled receptors. Proc Natl Acad Sci USA. 20 Feb 15, 2000; 97(4): 1489-94. .sup.472 Elorza A, Sarnago S, Mayor F Jr. Agonist-dependent modulation of G protein-coupled receptor kinase 2 by mitogen-activated protein kinases. Mol Pharmacol. 2000 Apr; 57(4): 778-83. .sup.473 Luttrell L M, Ferguson S S, Daaka Y, Miller W E, Maudsley S, Delia Rocca G J, Lin F, Kawakatsu H, Owada K, Luttrell D K, Caron M G, Lefkowitz R J. Beta-arrestin-dependent formation of beta2 adrenergic receptor-Src protein kinase complexes. Science. 1999 Jan 29; 283(5402): 655-61. .sup.474 Daaka Y, Luttrell L M, Ahn S, Delia Rocca G J, Ferguson S S, Caron M G, Lefkowitz R J. Essential role for G protein-coupled receptor endocytosis in the activation of mitogen-activated protein kinase. J Biol Chem. 1998 Jan 9; 273(2): 685-8. .sup.475 Cao W, Luttrell L M, Medvedev A V, Pierce K L, Daniel K W, Dixon T M, Lefkowitz R J, Collins S. Direct Binding of **Activated c-Src** to the Beta3-Adrenergic Receptor is Required for MAP Kinase Activation. J Biol Chem. 2000 Sep 29. .sup.476 Gerhardt C C, Gros J, Strosberg A D, Issad T. Stimulation of the extracellular signal-regulated kinase #E,FRA;1/2#EE; pathway by human beta-3 adrenergic receptor: new pharmacological profile and mechanism of activation. Mol Pharmacol. 1999 Feb; 55(2): 255-62. .sup.477 Soeder K J, Snedden S K, Cao W, Delia Rocca G J, Daniel K W, Luttrell L M, Collins S. The beta3- adrenergic receptor activates mitogen-activated protein kinase in adipocytes through a Gi-dependent mechanism. J Biol Chem. 1999 Apr 23; 274(17): 12017-22. .sup.478 Hellstrom L, Langin D, Reynisdottir S, Dauzats M, Arner P. Adipocyte lipolysis in normal weight subjects with obesity among first-degree relatives. Diabetologia. 1996 Aug; 39(8): 921-8. .sup.479 Shimizu Y, Tanishita T, Minokoshi Y, Shimazu T. Activation of mitogen-activated protein kinase by norepinephrine in brown adipocytes from rats. Endocrinology. 1997 Jan; 138(1): 248-53. .sup.480 Yarwood S J, Kilgour E, Anderson N G. Cyclic AMP stimulates the phosphorylation and activation of p42 and p44 mitogen-activated protein kinases in 3T3-F442A preadipocytes. Biochem Biophys Res Commun. 1996 Jul 25; 224(3): 734-9. .sup.481 Gerhardt C C, Gros J, Strosberg A D, Issad T. Stimulation of the extracellular signal-regulated kinase #E,FRA;1/2#EE; pathway by human beta-3 adrenergic receptor: new pharmacological profile and mechanism of activation. Mol Pharmacol. 1999 Feb; 55(2): 255-62. .sup.482 Hellstrom L, Reynisdottir S. Influence of heredity for obesity on adipocyte lipolysis in lean and obese subjects. Int J Obes Relat Metab Disord. 2000 Mar; 24(3): 340-4. .sup.483 Bougneres P, Stunff C L, Pecqueur C, Pinglier E, Adnot P, Ricquier D. In vivo resistance of lipolysis to epinephrine. A new feature of childhood onset obesity. J Clin Invest. 1997 Jun 1; 99(11): 2568-73. .sup.484 Horowitz J F, Klein S. Whole body and abdominal lipolytic sensitivity to epinephrine is suppressed in upper body obese women. Am J Physiol Endocrinol Metab. 2000 Jun; 278(6): E1144-52. .sup.485 Osuga J, Ishibashi S, Oka T, Yagyu H, Tozawa R, Fujimoto A, Shionoiri F, Yahagi N, Kraemer F B, Tsutsumi O, Yamada N. Targeted disruption of hormone-sensitive lipase results in male sterility and adipocyte hypertrophy, but not in obesity. Proc Natl Acad Sci USA. 2000 Jan 18; 97(2): 787-92. .sup.486 Classon M, Kennedy B K, Mulloy R, Harlow E. Opposing roles of pRB and p107 in adipocyte differentiation. Proc Natl Acad Sci USA. 2000 Sep 26; 97(20): 10826-31. .sup.487 Puigserver P, Ribot J, Serra F, Gianotti M, Bonet M L, Nadal-Ginard B, Palou A. Involvement of the retinoblastoma protein in brown and white adipocyte cell differentiation: functional and physical association with the adipogenic transcription factor C/EBPalpha. Eur J Cell Biol. 1998

Oct; 77(2): 117-23. .sup.488 Roncari D A, Kindler S, Hollenberg C H. Excessive proliferation in culture of reverted adipocytes from massively obese persons. Metabolism. 1986 Jan; 35(1): 1-4. .sup.489 Roncari D A, Lau D C, Kindler S. Exaggerated replication in culture of adipocyte precursors from massively obese persons. Metabolism. 1981 May; 30(5): 425-7. .sup.490 Stock S, Granstrom L, Backman L, Matthiesen A S, Uvnas-Moberg K. Elevated plasma levels of oxytocin in obese subjects before and after gastric banding. Int J Obes. 1989; 13(2): 213-22. .sup.491 Johnson S R, Kolberg B H, Varner M W, Railsback L D. Maternal obesity and pregnancy. Surg Gynecol Obstet. 1987 May; 164(5): 431-7. .sup.492 Yakinci C, Pac A, Kucukbay F Z, Tayfun M, Gul A. Serum zinc, copper, and magnesium levels in obese children. Acta Paediatr Jpn. 1997 Jun; 39(3): 339-41. .sup.493 D'Ocon C, Alonso de Armino V, Frasquet I. Levels of Zn and Cu in the serum of a diabetic population. Rev Esp Fisiol. 1987 Sep; 43(3): 335-8. Spanish. .sup.494 Taneja S K, Mahajan M, Arya P. Excess bioavailability of zinc may cause obesity in humans. Experientia. 1996 Jan 16; 52(1): 31-3. .sup.495 Ludvik B, Nolan J J, Baloga J, Sacks D, Olefsky J. Effect of obesity on insulin resistance in normal subjects and patients with NIDDM. Diabetes. 1995 Sep; 44(9): 1121-5. .sup.496 Prager R, Wallace P, Olefsky J M. Hyperinsulinemia does not compensate for peripheral insulin resistance in obesity. Diabetes. 1987 Mar; 36(3): 327-34. .sup.497 Tasaka Y, Yanagisawa K, Iwamoto Y. Human plasma leptin in obese subjects and diabetics. Endocr J. 1997 Oct; 44(5): 671-6. .sup.498 Bjorbaek C, El-Haschimi K, Frantz J D, Flier J S. The role of SOCS-3 in leptin signaling and leptin resistance. J Biol Chem. 1999 Oct 15; 274(42): 30059-65. .sup.499 de Waard F, Poortman J, de Pedro-Alvarez Ferrero M, Baanders-van Halewijn E A. Weight reduction and oestrogen excretion in obese post-menopausal women. Maruritas. 1982 Aug; 4(2): 155-62. .sup.500 Cauley J A, Gutai J P, Kuller L H, LeDonne D, Powell J G. The epidemiology of serum sex hormones in postmenopausal women. Am J Epidemiol. 1989 Jun; 129(6): 1120-31. .sup.501 Cauley J A, Gutai J P, Kuller L H, Scott J, Nevitt M C. Black-white differences in serum sex hormones and bone mineral density. Am J Epidemiol. 1994 May 15; 139(10): 1035-46. .sup.502 Galea J, Armstrong J, Gadsdon P, Holden H, Francis S E, Holt C M. Interleukin-1 beta in coronary arteries of patients with ischemic heart disease. Arterioscler Thromb Vasc Biol. 1996 Aug; 16(8): 1000-6. .sup.503 Hasdai D, Scheinowitz M, Leibovitz E, Sclarovsky S, Eldar M, Barak V. Increased serum concentrations of interleukin-1 beta in patients with coronary artery disease. Heart. 1996 Jul; 76(1): 24-8. .sup.504 Pickup J C, Mattock M B, Chusney G D, Burt D. NIDDM as a disease of the innate immune system: association of acute-phase reactants and interleukin-6 with metabolic syndrome X. Diabetologia. 1997 Nov; 40(11): 1286-92. .sup.505 Pickup J C, Crook M A. Is type II diabetes mellitus a disease of the innate immune system? Diabetologia. 1998 Oct; 41(10): 1241-8. .sup.506 Hrnciar J, Gabor D, Hrnciarova M, Okapcova J, Szentivanyi M, Kurray P. [Relation between cytokines (TNF-alpha, IL-1 and 6) and homocysteine in android obesity and the phenomenon of insulin resistance syndromes]. Vnitr Lek. 1999 Jan; 45(1): 11-6. Slovak. .sup.507 Klein J B, Rane M J, Scherzer J A, Coxon PY, Kettritz R, Mathiesen J M, Buridi A, McLeish K R. Granulocyte-macrophage colony-stimulating factor delays neutrophil constitutive apoptosis through phosphoinositide 3-kinase and extracellular signal-regulated kinase pathways. J Immunol 2000 Apr 15; 164(8): 4286-91. .sup.508 Valledor A F, Comalada M, Xaus J, Celada A. The differential time-course of extracellular-regulated kinase activity correlates with the macrophage response toward proliferation or activation. J Biol Chem 2000 Mar 10; 275(10): 7403-9. .sup.509 Thomas R S, Tymms M J, McKinlay L H,

Shannon M F, Seth A, Kola I. ETS1, NFkappaB and AP1 synergistically transactivate the human GM-CSF promoter. Oncogene. 1997 Jun 12; 14(23): 2845-55. .sup.510 Dhurandhar N V, Israel B A, Kolesar J M, Mayhew G F, Cook M E, Atkinson R L. Increased adiposity in animals due to a human virus. Int J Obes Relat Metab Disord. 2000 Aug; 24(8): 989-96. .sup.511 Behrens G M, Stoll M, Schmidt R E. Lipodystrophy syndrome in HIV infection: what is it, what causes

PGPUB-DOCUMENT-NUMBER: 20030096816

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030096816 A1

TITLE: Inhibitors of c-Jun N-terminal kinases (JNK) and other protein kinases

PUBLICATION-DATE: May 22, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Cao, Jingrong	Newton	MA	US	
Green, Jeremy	Burlington	MA	US	
Moon, Young-Choon	Lexington	MA	US	
Wang, Jian	Boston	MA	US	
Ledeboer, Mark	Acton	MA	US	
Harrington, Edmund	South Boston	MA	US	
Gao, Huai	Natick	MA	US	

APPL-NO: 10/ 121035

DATE FILED: April 10, 2002

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60283621 20010413 US

non-provisional-of-provisional 60329440 20011015 US

non-provisional-of-provisional 60292974 20010523 US

US-CL-CURRENT: 514/242, 514/252.01 , 514/275 , 544/182 , 544/238 , 544/331

ABSTRACT:

The present invention provides compounds of formula I: 1
or a pharmaceutically acceptable derivative o thereof, wherein A, B, R.sup.a, R.sup.1, R.sup.2, R.sup.3, and R.sup.4 are as described in the specification. These compounds are inhibitors of protein kinase, particularly inhibitors of JNK, a mammalian protein kinase involved cell proliferation, cell death and response to extracellular stimuli; Lck and Src kinase. The invention also relates to methods for producing these inhibitors. The invention also provides pharmaceutical compositions comprising the inhibitors of the invention and methods of utilizing those compositions in the treatment and prevention of various disorders.

CROSS REFERENCE TO RELATED APPLICATIONS

[0001] This application claims benefit of priority to co-pending U.S.

provisional applications 60/283,621 filed Apr. 13, 2001, 60/329,440 filed Oct. 14, 2001 and 60/292,974 filed May 23, 2001.

---------- KWIC ---------

Summary of Invention Paragraph - BSTX (19):
[0018] Src also plays a role in the replication of hepatitis B virus. The virally encoded transcription factor **HBx activates Src** in a step required for propagation of the virus. Klein et al., EMBO J., 18, 5019, (1999) and Klein et al., Mol.Cell. Biol., 17, 6427 (1997).

Summary of Invention Paragraph - BSTX (22):
[0021] Accordingly, there is still a great need to develop potent inhibitors of JNKs and Src family kinases that are useful in treating various conditions associated with JNK and **Src activation**.

Summary of Invention Paragraph - BSTX (214):
[0211] The activity of the compounds of this invention as kinase inhibitors may be assayed in vitro, in vivo or in a cell line. In vitro assays include assays that determine inhibition of either the kinase activity or ATPase activity of **activated enzyme, for example JNK, Lck, or Src**. Alternate in vitro assays quantitate the ability of the inhibitor to bind to JNK, Lck, or Src and may be measured either by radiolabelling the inhibitor prior to binding, isolating the inhibitor/JNK, inhibitor/Lck, or inhibitor/Src complex and determining the amount of radiolabel bound, or by running a competition experiment where new compounds are incubated with JNK, Lck, or Src bound to known radioligands. One may use any type or isoform of JNK, Lck, or Src, depending upon which JNK, Lck, or Src type or isoform is to be inhibited. The details of the conditions used for the enzymatic assays are set forth in the Examples hereinbelow.

PGPUB-DOCUMENT-NUMBER: 20030092601

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030092601 A1

TITLE: Microcompetition and human disease

PUBLICATION-DATE: May 15, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Polansky, Hanan	Rochester	NY	US	

APPL-NO: 09/ 732360

DATE FILED: December 7, 2000

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60169518 19991207 US

non-provisional-of-provisional 60183184 20000217 US

US-CL-CURRENT: 514/1

ABSTRACT:

Cellular microcompetition for the transcription factor human GA binding protein (GABP) is a risk factor associated with obesity and obesity-related diseases such as osteoarthritis, atherosclerosis, obstructive sleep apnea, various cancers, and periodontitis. The invention uses this novel discovery to develop assays which determine the level of microcompetition in a cell. Other assays developed from the knowledge that microcompetition is occurring in cells are also disclosed. This novel discovery led to the development of assays which can determine the level of microcompetition in a cell and to select compounds to target this microcompetition syndrome. In addition, methods to treat a patient for microcompetition based disease are taught.

---------- KWIC ---------

Detail Description Paragraph - DETX (413):

[0435] The fourth point requires an understanding of the "mechanisms of virus mediated cell transformation." Crawford (1986.sup.312) and Butel (2000.sup.313) also emphasize the significance of understanding the mechanism in attributing a causality role to infection. According to Crawford: "one alternative approach to understudying the role of the papillomaviruses in cervical carcinoma is to identify the mechanisms by which this group of viruses may induce the malignant transformation of normal cells." According to Butel:

"molecular studies detected viral markers in tumors, but the mechanism of **HBV** involvement in liver carcinogenesis remains the subject of investigation today." When the other kind of evidence is in place, understanding the mechanism turns a mere association into a causal relation.

Detail Description Paragraph - DETX (1024):

[1042] .sup.359 Cao W, Luttrell L M, Medvedev A V, Pierce K L, Daniel K W, Dixon T M, Lefkowitz R J, Collins S. Direct Binding of **Activated c-Src** to the Beta3-Adrenergic Receptor is Required for MAP Kinase Activation. J Biol Chem. Sep. 29, 2000.

Detail Description Table CWU - DETL (4):

4 Virus Cancer Epstein-Bar virus (EBV) Burkitt's lymphoma (BL) Nasopharyngeal carcinoma (NPC) Hodgkin's disease Some T-cell lyphomas Polymorphic B cell lymphomas B-cell lymphoproliferation in immunosuppressed individuals Breast cancer SV40 Brain tumors Osteosacromas Mesotheliomas HIV Brest cancer Human T cell lymphotrophic Adult T-cell leukemia virus-I (HTLV-I) Human papilloma virus Anogenital cancers (HPV) Skin cancers Oral cancers Hepatitis B virus (**HBV**) Hepatocellular carcinoma Hepatitis C virus (HCV) Hepatocellular carcinoma Human herpes virus 8 Kaposi's sarcoma, (HHV8, KSHV) Body cavity lymphoma

PGPUB-DOCUMENT-NUMBER: 20030087922

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030087922 A1

TITLE: Inhibitors of c-Jun N-terminal kinases (JNK) and other protein kinases

PUBLICATION-DATE: May 8, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Bethiel, Randy S.	Arlington	MA	US	
Cochran, John	North Andover	MA	US	
Moon, Young-Choon	Lexington	MA	US	
Nanthakumar, Suganthini	Newton	MA	US	

APPL-NO: 10/ 109070

DATE FILED: March 28, 2002

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60279961 20010329 US

US-CL-CURRENT: 514/275, 544/330 , 544/331

ABSTRACT:

The present invention provide a compound of formula I or II: 1
or a pharmaceutically acceptable derivative thereof, wherein R.sup.1, R.sup.2, R.sup.3, and R.sup.4 are as described in the specification. These compounds are inhibitors of protein kinase, particularly inhibitors of JNK, a mammalian protein kinase involved cell proliferation, cell death and response to extracellular stimuli; and Src-family kinases, especially Src and Lck kinases. These compounds are also inhibitors of GSK3 and CDK2 kinases. The invention also relates to methods for producing these inhibitors. The invention also provides pharmaceutical compositions comprising the inhibitors of the invention and methods of utilizing those compositions in the treatment and prevention of various disorders.

CROSS REFERENCE TO RELATED APPLICATION

[0001] This application claims priority to U.S. Provisional Patent Application No. 60/279,961 filed Mar. 29, 2001, the contents of which is incorporated herein by reference.

---------- KWIC ---------

Summary of Invention Paragraph - BSTX (2):

[0002] The present invention relates to inhibitors of protein kinase, especially c-Jun N-terminal kinases (JNK) and **Src-family of kinases, which are members of the mitogen-activated** protein (MAP) kinase family. There are a number of different genes and isoforms which encode JNKs. Members of the JNK family regulate signal transduction in response to environmental stress and proinflammatory cytokines and have been implicated in the mediation of a number of different disorders. Members of the Src family are implicated in a number of human diseases. The invention also relates to inhibitors of GSK3 kinase, which is implicated in diabetes and other disorders, and CDK2 kinase which plays a role in the regulation of the cell division cycle. The invention also provides pharmaceutical compositions comprising the inhibitors of the invention and methods of utilizing those compositions in the treatment and prevention of various disorders.

Summary of Invention Paragraph - BSTX (20):

[0019] Src also plays a role in the replication of hepatitis B virus. The virally encoded transcription factor **HBx activates Src** in a step required for propagation of the virus. Klein et al., EMBO J., 18, 5019, (1999) and Klein et al., Mol. Cell. Biol., 17, 6427 (1997).

Summary of Invention Paragraph - BSTX (34):

[0033] Accordingly, there is still a great need to develop potent inhibitors of JNKs and Src family kinases, including JNK3, Src, and Lck inhibitors, and of GSK3 and CDK2 inhibitors that are useful in treating various diseases or conditions associated with JNK3, **Src, Lck, GSK3, and CDK2 activation**.

PGPUB-DOCUMENT-NUMBER: 20030069199

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030069199 A1

TITLE: Treatment methods based on microcompetition for a limiting GABP complex

PUBLICATION-DATE: April 10, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Polansky, Hanan	Rochester	NY	US	

APPL-NO: 10/ 219334

DATE FILED: August 15, 2002

RELATED-US-APPL-DATA:

child 10219334 A1 20020815

parent continuation-in-part-of 09732360 20001207 US PENDING

US-CL-CURRENT: 514/44, 424/186.1 , 424/93.2

ABSTRACT:

Microcompetition for GABP between a foreign polynucleotide and a cellular GABP regulated gene is a risk factor associated with chronic disease such as obesity, cancer, atherosclerosis, stroke, osteoarthritis, diabetes, asthma, and other autoimmune diseases. The invention uses this novel discovery to present methods for the treatment of these chronic diseases. The methods are based on modifying such microcompetition, or the effect of such microcompetition on the cell. For instance, treatment may modify the cellular copy number of the foreign polynucleotide, change the rate of complex formation between GABP and either the foreign polynucleotide or the cellular GABP regulated gene, vary the expression of the cellular GABP regulated gene, or manipulate the activity of the gene product of the cellular GABP regulated gene. The invention also presents methods for treatment of chronic diseases resulting from other foreign polynucleotide-type disruptions.

---------- KWIC ---------

Detail Description Paragraph - DETX (323):

[0376] Another p300/cbp factor is NF-Y (see above). Mantovani 1998 (ibid) provides a list of viruses which include a NF-Y binding site (Table 1). The list includes **HBV** S, MSV LTR, RSV LTR, ad EIIL II, Ad MK, CMV gpUL4, HSV

IE110k, VZV ORF62, MVM P4.

Detail Description Paragraph - DETX (1535):
[1587] The fourth point requires an understanding of the "mechanisms of virus mediated cell transformation." Crawford (1986.sup.435) and Butel (2000, ibid) also emphasize the significance of understanding the mechanism in attributing a causal role to infection. According to Crawford: "one alternative approach to understanding the role of the papillomaviruses in cervical carcinoma is to identify the mechanisms by which this group of viruses may induce the malignant transformation of normal cells." According to Butel: "molecular studies detected viral markers in tumors, but the mechanism of **HBV** involvement in liver carcinogenesis remains the subject of investigation today." When the other kind of evidence is in place, understanding the mechanism turns a mere association into a causal relation.

Detail Description Paragraph - DETX (2542):
[2592] .sup.475 Cao W, Luttrell L M, Medvedev A V, Pierce K L, Daniel K W, Dixon T M, Lefkowitz R J, Collins S. Direct Binding of **Activated c-Src** to the Beta3-Adrenergic Receptor is Required for MAP Kinase Activation. J Biol Chem. 2000 Sep 29.

Detail Description Table CWU - DETL (7):
5 Virus Cancer Epstein-Bar virus (EBY) Burkitt's lymphoma (BL) Nasopharyngeal carcinoma (NPC) Hodgkin's disease Some T-cell lyphomas Polymorphic B cell lymphomas B-cell lymphoproliferation in immunosuppressed individuals Breast cancer SV40 Brain tumors Osteosacromas Mesotheliomas HIV Breast cancer Human T cell lymphotrophic Adult T-cell leukemia virus - I (HTLV-I) Human papilloma virus Anogenital cancers (HPV) Skin cancers Oral cancers Hepatitis B virus (**HBV**) Hepatocellular carcinoma Hepatitis C virus (HCV) Hepatocellular carcinoma Human herpes virus 8 Kaposi's sarcoma, (HHV8, KSHV) Body cavity lymphoma

PGPUB-DOCUMENT-NUMBER: 20030068616

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030068616 A1

TITLE: Drug discovery assays based on microcompetition for a limiting GABP complex

PUBLICATION-DATE: April 10, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Polansky, Hanan	Rochester	NY	US	

APPL-NO: 10/ 223050

DATE FILED: August 14, 2002

RELATED-US-APPL-DATA:

child 10223050 A1 20020814

parent continuation-in-part-of 09732360 20001207 US PENDING

US-CL-CURRENT: 435/5, 435/320.1 , 435/325 , 435/366 , 435/456 , 435/7.21

ABSTRACT:

A recent discovery showed that microcompetition for GABP between a foreign polynucleotide and a cellular GABP regulated gene is a risk factor for some of the major chronic diseases, such as obesity, cancer, atherosclerosis, stroke, osteoarthritis, diabetes, asthma, and other autoimmune diseases. The invention uses this novel discovery to present assays for screening compounds based on their effectiveness in modulating such microcompetition, or the effects of such microcompetition on the cell. The selected compounds can be used in treatment of these chronic diseases. The invention also presents assays for screening compounds that can be used in treatment of chronic diseases resulting from other foreign polynucleotide-type disruptions.

---------- KWIC ---------

Detail Description Paragraph - DETX (324):

[0356] Another p300/cbp factor is NF-Y (see above). Mantovani 1998 (ibid) provides a list of viruses which include a NF-Y binding site (Table 1). The list includes **HBV** S, MSV LTR, RSV LTR, ad EIIL II, Ad MK, CMV gpUL4, HSV IE IOk, VZV 0RF62, MVM P4.

Detail Description Paragraph - DETX (1545):

[1566] The fourth point requires an understanding of the "mechanisms of virus mediated cell transformation." Crawford (1986.sup.435) and Butel (2000, ibid) also emphasize the significance of understanding the mechanism in attributing a causal role to infection. According to Crawford: "one alternative approach to understanding the role of the papillomaviruses in cervical carcinoma is to identify the mechanisms by which this group of viruses may induce the malignant transformation of normal cells." According to Butel: "molecular studies detected viral markers in tumors, but the mechanism of **HBV** involvement in liver carcinogenesis remains the subject of investigation today." When the other kind of evidence is in place, understanding the mechanism turns a mere association into a causal relation.

Detail Description Paragraph - DETX (2553):

[2572] .sup.475 Cao W, Luttrell L M, Medvedev A V, Pierce K L, Daniel K W, Dixon T M, Lefkowitz R J, Collins S. Direct Binding of **Activated c-Src** to the Beta3-Adrenergic Receptor is Required for MAP Kinase Activation. J. Biol. Chem. Sep. 29, 2000.

Detail Description Table CWU - DETL (8):

5 Virus Cancer Epstein-Bar virus (EBV) Burkitt's lymphoma (BL) Nasopharyngeal carcinoma (NPC) Hodgkin's disease Some T-cell lyphomas Polymorphic B cell lymphomas B-cell lymphoproliferation in immunosuppressed individuals Breast cancer SV40 Brain tumors Osteosacromas Mesotheliomas HIV Breast cancer Human T cell lymphotrophic Adult T-cell leukemia virus-I (HTLV-I) Human papilloma virus (HPV) Anogenital cancers Skin cancers Oral cancers Hepatitis B virus (**HBV**) Hepatocellular carcinoma Hepatitis C virus (HCV) Hepatocellular carcinoma Human herpes virus 8 Kaposi's sarcoma, (HHV8, KSHV) Body cavity lymphoma

PGPUB-DOCUMENT-NUMBER: 20030049649

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030049649 A1

TITLE: Targeted modification of chromatin structure

PUBLICATION-DATE: March 13, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Wolffe, Alan P.	San Pablo	CA	US	
Wolffe, Elizabeth J.	Richmond	CA	US	
Collingwood, Trevor			US	
Snowden, Andrew			US	

APPL-NO: 10/ 084826

DATE FILED: February 24, 2002

RELATED-US-APPL-DATA:

child 10084826 A1 20020224

parent continuation-in-part-of 09844508 20010427 US PENDING

non-provisional-of-provisional 60200590 20000428 US

non-provisional-of-provisional 60228523 20000828 US

US-CL-CURRENT: 435/6, 435/199 , 435/455 , 435/468

ABSTRACT:

Methods and compositions for targeted modification of chromatin structure, within a region of interest in cellular chromatin, are provided. Such methods and compositions are useful for facilitating processes such as, for example, transcription and recombination, that require access of exogenous molecules to chromosomal DNA sequences.

CROSS-REFERENCE TO RELATED APPLICATIONS

[0001] This application is a continuation-in-part of copending U.S. patent application Ser. No. 09/844,508 (filed Apr. 27, 2001), which in turn claims priority to U.S. Provisional Patent Application Serial No. 60/200,590, filed Apr. 28, 2000 and to U.S. Provisional Patent Application Serial No. 60/228,523, filed Aug. 28, 2000. The disclosures of all of the aforementioned patent applications are hereby incorporated by reference in their entireties.

---------- KWIC ---------

Detail Description Paragraph - DETX (122):

[0155] Numerous HAT enzymes have been described, including budding yeast Gcn5p, which is required for expression of a subset of the yeast genome, its mammalian orthologue CREB-binding protein (CBP), p300 (both of the latter two used as coactivators by a wide variety of mammalian transcription factors), TAF.sub.II250 (a component of the basal transcriptional machinery), and steroid receptor coactivator 1 (**SRC-1), which potentiates transcriptional activation** by a number of nuclear hormone receptors. Kouzarides (1999) supra; Cheung et al. (2000) Curr. Opin. Cell Biol. 12:326-333; and Sterner et al. (2000) supra.

Detail Description Paragraph - DETX (200):

[0227] Expression of human, mammalian, bacterial, fungal, protozoal, Archaeal, plant and viral genes can be modulated; viral genes include, but are not limited to, hepatitis virus genes such as, for example, **HBV**-C, **HBV**-S, **HBV**-X and **HBV**-P; and HIV genes such as, for example, tat and rev. Modulation of expression of genes encoding antigens of a pathogenic organism can be achieved using the disclosed methods and compositions.

Detail Description Paragraph - DETX (328):

Activation of EPO Expression by Fusion of SRC-1 to a Zinc Finger Binding Domain

PGPUB-DOCUMENT-NUMBER: 20030039957

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030039957 A1

TITLE: Functional protein expression for rapid cell-free phenotyping

PUBLICATION-DATE: February 27, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
McCarthy, Laurence	Great Falls	VA	US	
Kong, Lilly	Covina	CA	US	
Shao, Tang	Rosemead	CA	US	
Su, Xin	Irvine	CA	US	

APPL-NO: 09/ 996187

DATE FILED: November 27, 2001

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60253150 20001127 US

non-provisional-of-provisional 60297686 20010612 US

non-provisional-of-provisional 60304533 20010709 US

US-CL-CURRENT: 435/5, 435/6 , 435/7.1 , 435/7.32

ABSTRACT:

Disclosed herein are methods for assaying the phenotype of a bioactive molecule in the presence and absence of compounds that are known inhibitors of the phenotypable activity of the bioactive molecule. Also disclosed are methods for discovering compounds that can inhibit the phenotypable activity of a bioactive molecule. The methods and assays of the present invention are useful in developing and monitoring a chemotherapy regimen for a patient, to detect or prevent the emergence of a drug resistant phenotype.

RELATED APPLICATIONS

[0001] This application claims priority from U.S. provisional patents serial No. 60/253,150 filed Nov. 27, 2000, and serial No. 60/297,686 filed Jul. 12, 2001, incorporated herein by reference.

---------- KWIC ---------

Brief Description of Drawings Paragraph - DRTX (3):

[0019] FIG. 1 illustrates an assay measuring the DNA dependent DNA polymerase activity of both mutant (**HBV**-m)and wild-type (**HBV**-WT) variants of the hepatitis B virus.

Brief Description of Drawings Paragraph - DRTX (5):

[0021] FIG. 3 illustrates an inhibition curve of the anti-viral compound lamivudine-TP, and its effects on **HBV** polymerase activity over a concentration range of the drug as against the wild-type (**HBV**-WT) with a lamivudine sensitive phenotype and mutant **HBV** proteins with a lamivudine resistant phenotype (**HBV**-M, HM1, HM2, and HM5).

Detail Description Paragraph - DETX (14):

[0034] "Bioactive molecule" means a nucleic acid, ribonucleic acid, polypeptide, glycopolypeptide, mucopolysaccharide, lipoprotein, lipopolysaccharide, carbohydrate, enzyme or co-enzyme, hormone, chemokine, lymphokine, or similar compound, that involves, regulates, or is the rate-limiting compound in a biosynthetic reaction or metabolic or reproductive process in a microorganism or tissue. Such bioactive molecules are common therapeutic drug targets, and include for example and without limitation, interferon, TNF, v-Ras, c-Ras, reverse transcriptase, g-coupled protein receptors (GPCR's), Fc.epsilon.R's, Fc.gamma.R's, nicotinicoid receptors (nicotinic receptor, GABA.sub.A and GABA.sub.C receptors, glycine receptors, 5-HT.sub.3 receptors and some glutamate activated anionic channels), ATP-gated channels (also referred to as the P2X purinoceptors), glutamate activated cationic channels (NMDA receptors, AMPA receptors, Kainate receptors, etc.), hemagglutinin (HA), receptor-tyrosine kinases (RTK's) such as EGF, PDGF, NGF and insulin receptor tyrosine kinases, SH2-domain proteins, PLC-.gamma., c-Ras-associated GTPase activating protein (RasGAP), phosphatidylinositol-3-kinase (PI-3K) and protein phosphatase 1C (PTP1C), as well as intracellular protein tyrosine kinases (PTK's), such as the **Src family of tyrosine kinases, glutamate activated** cationic channels (NMDA receptors, AMPA receptors, Kainate receptors, etc.), protein-tyrosine phosphatases Examples of receptor tyrosine phosphatases include: receptor tyrosine phosphatase rho, protein tyrosine phosphatase receptor J, receptor-type tyrosine phosphatase D30, protein tyrosine phosphatase receptor type C polypeptide associated protein, protein tyrosine phosphatase receptor-type T, receptor tyrosine phosphatase gamma, leukocyte-associated Ig-like receptor ID isoform, LAIR-1D, LAIR-1C, MAP kinases, neuraminadase (NA), proteases, polymerases, serine/threonine kinases, second messengers, transcription factors, and other such important metabolic building blocks or regulators. Virtually any bioactive molecule can be monitored with the present invention.

Detail Description Paragraph - DETX (27):

[0046] FIG. 1 illustrates an assay measuring the DNA dependent DNA polymerase activity of both mutant and wild-type variants of the hepatitis B virus (**HBV**). The DNA polymerase assay as shown provides a non-radioactive assay, which measures the ability of the enzyme to incorporate modified nucleotides into freshly synthesized DNA. The detection of synthesized DNA as

a parameter for DNA polymerase activity follows a sandwich ELISA protocol. The absorbence the samples is directly correlated to the level of DNA polymerase activity in the sample. **HBV**-WT refers to the wild-type **HBV** polymerase. **HBV**-M refers to an **HBV** polymerase containing a type-I mutation (L528M and M552V), that is phenotypicaly associated with lamivudine resistance. PC and NC refer respectively to positive and negative controls (see, Example 1).

Detail Description Paragraph - DETX (28):

[0047] FIG. 2 illustrates an inhibition curve of the anti-viral compound lamivudine-TP, and its effects on wild-type **HBV** polymerase activity over a concentration range of the drug. Lamivudine-TP was added to the polymerase assay across a final concentration range of 0, 20, 40, 60, 80, 100, 200, and 300 nM. Inhibition of DNA polymerase activity (%) was plotted against drug concentration. The curve defines the enzymes sensitivity across the compounds range.

Detail Description Paragraph - DETX (29):

[0048] FIG. 3 illustrates an inhibition curve of the anti-viral agent lamivudine-TP, and its effects on **HBV** polymerase activity over a concentration range of the drug as against the wild-type **HBV** polymerase (**HBV**-WT), the type-I mutant **HBV** protein (**HBV**-M, HM2 and HM5), and the type-II mutants (HM1 and HM3, displaying M552I and also phenotypically associated with lamivudine resistance). Lamivudine-TP was added to the polymerase assay across a final concentration range of 0, 60, 100, and 200 nM. Inhibition of DNA polymerase activity (%) was plotted against drug concentration. Thus, a phenotype and a sensitive resistant phenotype for **HBV** polymerase to lamivudine is detected.

Detail Description Paragraph - DETX (36):

[0054] Either DNA or RNA target sequences can be amplified by PCR. In the case of an RNA target, such as in the amplification of **HBV** nucleic acid as described herein, the first step consists of the synthesis of a DNA copy (cDNA) of the target sequence. The reverse transcription can be carried out as a separate step, or preferably in a combined reverse transcription-polymerase chain reaction (RT-PCR), a modification of the polymerase chain reaction for amplifying RNA. The RT-PCR amplification of RNA is well known in the art and described in U.S. Pat. Nos. 5,322,770 and 5,310,652; Myers and Gelfand, Biochemistry 30(31): 7661-7666 (1991); Young et al., J. Clin. Microbiol. 31(4): 882-886 (1993); and Young et al., J. Clin. Microbiol. 33(3): 654-657 (1995); each incorporated herein by reference.

Detail Description Paragraph - DETX (43):

[0061] Oligonucleotide primers can be prepared by any suitable method, including, for example, cloning and restriction of appropriate sequences and direct chemical synthesis by a method such as the phosphotriester method of Narang et al., 1979, Meth. Enzymol. 68: 90-99; the phosphodiester method of Brown et al., 1979, Meth. Enzyme. 68: 109-151; the diethylphosphoramidite method of Beaucage et al., 1981, Tetrahedron Lett. 22: 1859-1862; and the solid support method of U.S. Pat. No. 4,458,066, each incorporated herein by reference. Methods for synthesizing labeled oligonucleotides are described in

Agrawal and Zamecnik, 1990, Nucl. Acids. Res. 18(18): 5419-5423; MacMillan and Verdine, 1990, J. Org. Chem. 55: 5931-5933; Pieles et al., 1989, Nucl. Acids. Res. 17(22): 8967-8978; Roget et al., 1989, Nucl. Acids. Res. 17(19): 7643-7651; and Tesler et al., 1989, J. Am. Chem. Soc. 111: 6966-6976, each incorporated herein by reference. A review of synthesis methods is provided 1990, Bioconjugate Chemistry 1(3): 165-187, incorporated herein by reference. Table 1 illustrates a nested primer set of the present invention, used to amplify the viral gene encoding **HBV** polymerase. One or more secondary nucleic acid sequences may be added to the nucleic acid sequence encoding the bioactive molecule by PCR during the amplification steps depending on the experimental strategy, for example, these secondary nucleic acid sequences include His tags, HA or FLAG epitopes or other immunological based purification motifs, GST, streptaviden or MBP proteins, nucleic acid sequences or other purification motifs. Methods of purification of recombinant proteins are well described, and such methods applicable to the invention include metal chelate chromatography, affinity chromatography, size exclusion chromatography, anion exchange chromatography, and cation exchange chromatography. These purification techniques can also be employed with such chromatography systems as a gas chromatograph, HPLC or FPLC. The secondary nucleic acid sequences may comprise sequences encoding regulatory elements that modulate transcription or translation of the gene in the amplified nucleic acid, for example but not limited to, by adding a promoter such as ADH, T7, RSV, or CMV promoter, or by adding a Kozak sequence, or stem-loop termination sequences. Other reporter genes or domains may be used to create fusion proteins with the polypeptide of interest, for example, a GFP fusion protein or .beta.-galactosidase fusion protein. The invention also contemplates that multiple primer sets can be used to amplify one or more bioactive targets from a single reaction. The use of secondary nucleic acid sequences provides a particular advantage of the present invention where it is desirable that the nucleic acid sequences encoding the bioactive molecule are to be purified or cloned directly from a single PCR reaction that also generates the protein for the phenotypic assay.

Detail Description Paragraph - DETX (62):
Hepatitis B (**HBV**)

Detail Description Paragraph - DETX (63):
[0079] **HBV** is a causative agent for acute and chronic hepatitis, which strikes about 200 million patients worldwide (Zuckerman A. J., Trans. R. Soc. Trop. Med. Hygiene, 76: 711-718 (1982) incorporated by reference). **HBV** infection acquired in adult life is often clinically inapparent, and most acutely infected adults recover completely from the disease and clear the virus. Rarely, however, the acute liver disease may be so severe that the patient dies of fulminant hepatitis. A small fraction, perhaps 5-10%, of acutely infected adults, becomes persistently infected by the virus and develops chronic liver disease of varying severity. Neonatally transmitted **HBV** infection, however, is rarely cleared, and more than 90% of such children become chronically infected. Because **HBV** is commonly spread from infected mother to newborn infant in highly populated areas of Africa and Asia, several hundred million people throughout the world are persistently infected by **HBV** for most of their lives and suffer varying degrees of chronic liver disease, which greatly increases their risk of developing cirrhosis and hepatocellular

carcinoma (HCC). Indeed, the risk of HCC is increased 100-fold in patients with chronic hepatitis, and the lifetime risk of HCC in males infected at birth approaches 40%. Beasley R. P. et al., Lancet (1981) 2, 1129-1133. Incorporated by reference) Accordingly, a large fraction of the world's population suffers from and dies of these late complications of **HBV** infection. The development of anti-**HBV** drugs has been long awaited, but has been hampered by the extremely narrow host range of **HBV: HBV** replicates mainly in human and chimpanzee livers and not in experimental animals or in cultured cells. Tiollais, P et al., Nature (London) (1985) 317, 489-495 incorporated by reference.

Detail Description Paragraph - DETX (64):

[0080] Hepatitis B virus is a DNA virus with a compact genomic structure. Despite its small, circular, 3200 base pairs, **HBV** DNA codes for four sets of viral products and has a complex, multiparticle structure. **HBV** achieves its genomic economy by relying on an efficient strategy of encoding proteins from four overlapping genes: S, C, P, and X. **HBV** is one of a family of animal viruses, hepadnaviruses, and is classified as hepadnavirus type 1. Similar viruses infect certain species of woodchucks, ground and tree squirrels, and Peking ducks. All hepadnaviruses, including **HBV,** share the following characteristics: 1) three distinctive morphological forms exist, 2) all members have proteins that are functional and structural counterparts to the envelope and nucleocapsid antigens of **HBV,** 3) they replicate within the liver but can also exist in extrahepatic sites, 4) they contain an endogenous DNA polymerase with both RNA- and DNA-dependent DNA polymerase activities, 5) their genomes are partially double stranded circular DNA molecules, 6) they are associated with acute and chronic hepatitis and hepatocellular carcinoma and 7) replication of their genome goes through an RNA intermediate which is reverse transcribed into DNA using the virus's endogenous RNA-dependent DNA polymerase activity in a manner analogous to that seen in retroviruses. In the nucleus of infected liver cells, the partially double stranded DNA is converted to a covalently closed circular double stranded DNA (cccDNA) by the DNA-dependent DNA polymerase. Transcription of the viral DNA is accomplished by a host RNA polymerase and gives rise to several RNA transcripts that differ in their initiation sites but all terminate at a common polyadenylation signal. The longest of these RNAs acts as the pregenome for the virus as well as the message for the some of the viral proteins. Viral proteins are translated from the pregenomic RNAs, and the proteins and RNA pregenome are packaged into virions and secreted from the hepatocyte. Although **HBV** is difficult to cultivate in vitro, several cells have been successfully transfected with **HBV** DNA resulting in the in vitro production of **HBV** particles.

Detail Description Paragraph - DETX (65):

[0081] There are three particulate forms of **HBV**: non-infectious 22 nm particles, which appear as either spherical or long filamentous forms, and 42 nm double-shelled spherical particles which represent the intact infectious hepatitis B virion. The envelope protein, HBsAg, is the product of the S gene of **HBV** and is found on the outer surface of the virion and on the smaller spherical and tubular structures.

Detail Description Paragraph - DETX (66):
[0082] Upstream of the S gene open reading frame are the pre-S gene open reading frames, pre-S 1 and pre-S2, which code for the pre-S gene products, including receptors on the **HBV** surface for polymerized human serum albumin and the attachment sites for hepatocyte receptors. The intact 42 nm virion can be disrupted by mild detergents and the 27 .mu.m nucleocapsid core . particle isolated. The core is composed of two nucleocapsid proteins coded for by the C gene. The C gene has two initiation codons defining a core and a precore region. The major antigen expressed on the surface of the nucleocapsid core is coded for by the core region and is referred to as hepatitis B core antigen (HBcAg). Hepatitis B e antigen (HBeAg) is produced from the same C gene by initiation at the precore ATG.

Detail Description Paragraph - DETX (67):
[0083] Also packaged within the nucleocapsid core is a DNA polymerase, which directs replication and repair of **HBV** DNA. The DNA polymerase is coded for by the P gene, the third and largest of the **HBV** genes. The enzyme has both DNA-dependent DNA polymerase and RNA-dependent reverse transcriptase activities and is also required for efficient encapsidation of the pregenomic RNA. The fourth gene, X, codes for a small, non-particle-associated protein which has been shown to be capable of transactivating the transcription of both viral and cellular genes. The DNA polymerase gene was selected as a target in this assay.

Detail Description Paragraph - DETX (68):
[0084] Amplification of Human **HBV** DNA Polymerase

Detail Description Paragraph - DETX (69):
[0085] Viral DNA was isolated from **HBV** patient serum specimens with the QIAamp Blood Kit (Qiagen, Valencia, Calif.). A nested PCR procedure was used to amplify **HBV** DNA polymerase sequences encoding the wild-type **HBV** polymerase (**HBV**-WT), the type-I mutant **HBV** protein (**HBV**-M, HM2 and HM5) carrying the mutations L528M and M552V, and the type-II mutants (HM1 and HM3), carrying the mutation M5521. Both mutations are phenotypically associated with lamivudine resistance.

Detail Description Paragraph - DETX (71):
[0087] The resulting 2.6 kb PCR generated DNA templates contained a T7 RNA polymerase promoter sequence for transcribing the DNA, a Kozak consensus sequence for efficiently translating the RNA, and the specific **HBV** DNA polymerase sequences from the patient specimens.

Detail Description Paragraph - DETX (73):
[0089] The PCR-generated DNA templates were directly transcribed and translated in a cell-free expression system into **HBV** DNA polymerase using a rabbit reticulocyte lysate system, TNT T7 Quick for PCR DNA (Promega, Madison,

Wis.). A 90 kDa protein, corresponding to the full length **HBV** polymerase, was produced from this eukaryotic expression system

Detail Description Paragraph - DETX (75):

[0091] A sensitive DNA polymerase assay (Roche Molecular Biochemicals, Indianapolis, Ind.) was used to determine the DNA polymerase activity of the expressed **HBV** polymerase proteins. FIG. 1 measures the DNA dependent DNA polymerase activity of both mutant and wild-type variants of the hepatitis B virus (**HBV**). The DNA polymerase assay as shown provides a non-radioactive assay, which measures the ability of the enzyme to digoxigenin and biotin labeled nucleotides into freshly synthesized DNA. The detection of synthesized DNA as a parameter for DNA polymerase activity follows a sandwich ELISA protocol--biotin labeled nucleic acid binds the surface of a microtiter plate coated with streptavidin. An anti-digoxigenin antibody conjugated to peroxidase is incubated with the nucleic acid. Upon addition of the peroxidase substrate, a color change occurs corresponding to the peroxidase activity, which is detected by a microplate ELISA reader. The absorbance samples is directly correlated to the level of DNA polymerase activity in the sample. Such an assay is commercially available, for example, the DNA Polymerase, non-radioactive kit, from Roche Molecular Biochemicals. In FIG. 1, **HBV**-WT refers to the wild-type **HBV** polymerase. **HBV**-M refers to an **HBV** polymerase containing a type-I mutation (L528M and M552V), that is phenotypicaly associated with lamivudine resistance. PC and NC refer respectively to positive and negative controls. Briefly, the positive control includes Klenow enzyme in polymerase buffer. The negative control includes reticulcyte lysate without the DNA amplicon.

Detail Description Paragraph - DETX (76):

[0092] FIG. 2 illustrates an inhibition curve of the anti-viral compound lamivudine-TP, and its effects on **HBV** polymerase activity over a concentration range of the drug. Lamivudine-TP was used to contact the enzyme in the polymerase assay across a final concentration range of 0, 20, 40, 60, 80, 100, 200, and 300 nM. Inhibition of DNA polymerase activity (%) was plotted against compound concentration. Another technique of deriving the IC.sub.50 is to plot percent bioactivity against the log of the concentration of the inhibitor drug, in which case the inhibition curve is described by non-linear regression modeling using a single binding site algorithm. Such modeling programs are known in the art and include, for example, PRISM from GraphPad Software, (San Diego, Calif.).

Detail Description Paragraph - DETX (77):

[0093] FIG. 3 illustrates an inhibition curve of the anti-viral compound lamivudine-TP, and its effects on wild-type **HBV** polymerase activity over a concentration range of the drug as against the wild-type **HBV** polymerase (**HBV**-WT), the type-I mutant **HBV** protein (**HBV**-M, HM2 and HM5), and the type-II mutants (HM1 and HM3, displaying M552I and also phenotypically associated with lamivudine resistance). Lamivudine-TP was added to the polymerase assay across a final concentration range of 0, 60, 100, and 200 nM. Inhibition of DNA polymerase activity (%) was plotted against drug concentration. FIG. 1

illustrates an assay measuring the DNA dependent DNA polymerase activity of both mutant and wild-type variants of the hepatitis B virus (**HBV**). The DNA polymerase assay as shown provides a non-radioactive assay, which measures the ability of the enzyme to incorporate modified nucleotides into freshly synthesized DNA. The detection of synthesized DNA as a parameter for DNA polymerase activity follows a sandwich ELISA protocol. The absorbence the samples is directly correlated to the level of DNA polymerase activity in the sample. **HBV**-WT refers to the wild-type **HBV** polymerase. **HBV**-M refers to an **HBV** polymerase containing a type-I mutation (L528M and M552V), that is phenotypicaly associated with lamivudine resistance. PC and NC refer respectively to positive and negative controls.

PGPUB-DOCUMENT-NUMBER: 20030032596

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030032596 A1

TITLE: Inhibition of the Src kinase family pathway as a method of treating **HBV** infection and hepatocellular carcinoma

PUBLICATION-DATE: February 13, 2003

US-CL-CURRENT: 514/12, 514/262.1 , 514/44

APPL-NO: 10/ 196344

DATE FILED: July 15, 2002

RELATED-US-APPL-DATA:

child 10196344 A1 20020715

parent continuation-of 08874430 19970613 US GRANTED

parent-patent 6420338 US

PGPUB-DOCUMENT-NUMBER: 20030022196

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030022196 A1

TITLE: Methods and compositions for screening for altered cellular phenotypes

PUBLICATION-DATE: January 30, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Lorens, James	Portola Valley	CA	US	
Kinsella, Todd M.	Fayetteville	CA	US	
Masuda, Esteban	Menlo Park	CA	US	
Hitoshi, Yasumichi	Mountain view	CA	US	
Liao, X. Charlene	Palo Alto	CA	US	
Pearsall, Denise	Belmont	CA	US	
Friera, Annabelle	South San Francisco	CA	US	
Chu, Peter	San Francisco	CA	US	

APPL-NO: 10/ 096339

DATE FILED: March 8, 2002

RELATED-US-APPL-DATA:

child 10096339 A1 20020308

parent continuation-in-part-of 09076624 19980512 US PENDING

US-CL-CURRENT: 435/6, 435/325 , 435/455 , 435/7.21

ABSTRACT:

The invention relates to methods and compositions useful for screening for altered cellular phenotypes using an inducible expression system to enrich for and detect the altered phenotypes and, more particularly, relates to screening libraries of candidate bioactive agents, for example, nucleic acids and peptides, in cells using an regulatable expression system to enrich for a subpopulation of cells having an altered phenotype due to the presence of a candidate bioactive agent.

[0001] This application is a continuation-in-part of U.S. patent application Ser. No. 09/076,624, filed May 12, 1998 (pending).

---------- KWIC ---------

Detail Description Paragraph - DETX (209):

[0274] In a preferred embodiment, the present methods are useful in infectious disease applications. Viral latency (herpes viruses such as CMV, EBV, **HBV,** and other viruses such as HIV) and their reactivation are a significant problem, particularly in immunosuppressed patients (patients with AIDS and transplant patients). The ability to block the reactivation and spread of these viruses is an important goal. Cell lines known to harbor or be susceptible to latent viral infection can be infected with the specific virus, and then stimuli applied to these cells which have been shown to lead to reactivation and viral replication. This can be followed by measuring viral titers in the medium and scoring cells for phenotypic changes. Candidate libraries can then be inserted into these cells under the above conditions, and peptides isolated which block or diminish the growth and/or release of the virus. As with chemotherapeutics, these experiments can also be done with drugs which are only partially effective towards this outcome, and bioactive agents isolated which enhance the virucidal effect of these drugs.

Detail Description Paragraph - DETX (282):

[0337] Activation of specific signaling pathways in lymphocytes determines the quality, magnitude and duration of immune responses. In transplantation, acute and chronic inflammatory diseases, and autoimmunity, it is these pathways that are responsible for the induction, maintenance and exacerbation of disease lymphocyte responses. In all cases, recognition of antigens presented by the Major Histocompatability Complex (MHC) by the T cell receptor (TCR) complex triggers the activation of T lymphocytes. Engagement of the TCR by antigen/MHC results in actin cytoskeleton rearrangement, induction of cyrokine and other gene transcription, and progression into the cell cycle.sup.1,2. The proximal events of TCR signaling include **activation of src** family kinases LCK, FYN, phosphorylation of TCR component (.) and subsequent activation of ZAP70/SYK tyrosine kinases, as well as recruitmentof adaptormolecules(CBL-B, LAT, SLP76), which couple to more distal signaling pathways including Ras and PLC(.sup.3-5. New components of the TCR signaling pathway have been discovered and reported, such as the new transmembrane adaptor PAG/CBP.sup.6, albeit with a slower pace. It has become apparent that identifying additional signaling molecules requires novel approaches including functional genomics. Using the methods of the present invention, novel signaling molecules specific for T cell activation and effector function were identified and validated.

US-PAT-NO: 6579972

DOCUMENT-IDENTIFIER: US 6579972 B1

TITLE: Extracellular signal-regulated kinase, sequences, and methods of production and use

DATE-ISSUED: June 17, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Lechner; Cornelia	Unterschleissheim	N/A	N/A	DE
M.o slashed.ller; Niels Peter	Copenhagen	N/A	N/A	DK
Ullrich; Axel	Martinsreid	N/A	N/A	DE

APPL-NO: 09/ 393212

DATE FILED: September 9, 1999

PARENT-CASE:

RELATED APPLICATIONS

This application is a divisional of U.S. patent application Ser. No. 08/459,953, filed Jun. 2, 1995, now U.S. Pat. No. 6,030,822 by Lechner et al., and entitled "EXTRACELLULAR SIGNAL-REGULATED KINASE, SEQUENCES, AND METHODS OF PRODUCTION AND USE", which in turn is a continuation-in-part of U.S. application Ser. No. 08/029,404, filed Mar. 19, 1993, by Lechner et al., and entitled "EXTRACELLULAR SIGNAL-REGULATED KINASE, SEQUENCES, AND METHODS OF PRODUCTION AND USE," now U.S. Pat. No. 5,459,036, issued Oct. 17, 1995, both of which are hereby incorporated by reference herein in their entirety, including any drawings.

US-CL-CURRENT: 530/388.26, 435/7.92 , 530/388.1 , 530/389.1 , 530/809

ABSTRACT:

The present invention relates, in general, to an extracellular signal regulated kinase, ERK-5. In particular, the present invention relates to nucleic acid molecules coding for ERK-5; ERK-5 polypeptides; recombinant nucleic acid molecules; cells containing the recombinant nucleic acid molecules; antisense ERK-5 nucleic acid constructs; antibodies having binding affinity to an ERK-5 polypeptide; hybridomes containing the antibodies; nucleic acid probes for the detecting of ERK-5 nucleic acid; a method of detecting ERK-5 nucleic acid or polypeptide in a sample; kits containing nucleic acid probes or antibodies; a method of detecting a compound capable of binding to ERK-5 or a fragment thereof; a method of detecting an agonist or antagonist of ERK-5 activity; a method of agonizing or antagonizing ERK-5 associated activity in a mammal; a method of treating diabetes mellitus, skeletal muscle diseases,

Alzheimer's disease, or peripheral neuropathies in a mammal with an agonist or antagonist of ERK-5 activity; and a pharmaceutical composition comprising an ERK-5 agonist or antagonist.

10 Claims, 5 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 5

---------- KWIC ---------

Brief Summary Text - BSTX (13):

While some of these muscle specific transcription factors, namely MyoD and myf5, are constitutively expressed both in cycling myoblasts as well as in myotubes, myogenin expression is induced when myoblasts start to differentiate. However, not only transcriptional regulation, but also posttranslational modification such as phosphorylation which has been reported for MyoD1 and myogenin as well as myf5 may influence commitment to myogenesis and maintenance of the differentiated state. **Activated oncogenes like ras and src** as well as growth factors which are involved in or initiate signal transduction, inhibit myogenesis. In addition, PKC is able to phosphorylate myogenin and could be a major mediator of this inhibition.

Detailed Description Text - DETX (211):

NIH3T3 cells., immortalized mouse fibroblasts (Jainchill et al., J. Virol. 4:549-553 (1969)) were grown in DMEM with 4.5 mg/ml glucose and 10% FCS to subconfluency and transfected with 20 .mu.g/1.times.10.sup.7 cells of a cvn-construct containing the complete hERK-5 cDNA. The cvn vector carries the Sv40 early promoter, **HBV** poly A signal as well as a neomycin resistance gene which allows selection of transfected cells on G418 resistance, and the gene for the DHFR which can be used to increase the expression of the integrated cDNA by addition of methotrexate at concentrations of 100-1000 nM to the culture medium (Rosenthal et al., Cell 46:155-169 (1986)). Transfection was performed as described in Example 4. After 16 h at 35.degree. C. and 3% CO.sub.2, the medium was changed and the cells were grown at 37.degree. C., 5% CO.sub.2 for additional 24 h with one medium change after 8 h. The cells were then split to different dilutions and grown in 1 mg/ml G418 containing medium until cell colonies, appeared which were isolated and selected on methotrexate growth.

US-PAT-NO: 6576758

DOCUMENT-IDENTIFIER: US 6576758 B1

TITLE: Nucleic acid constructs containing hybrid promoters

DATE-ISSUED: June 10, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Seifart; Klaus-Heinrich	Marburg	N/A	N/A	DE
Mueller; Rolf	Marburg	N/A	N/A	DE
Sedlacek; Hans-Harald	Marburg	N/A	N/A	DE

APPL-NO: 08/ 936603

DATE FILED: September 24, 1997

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
DE	196 39 103	September 24, 1996

US-CL-CURRENT: 536/24.1, 435/320.1 , 536/23.1

ABSTRACT:

Nucleic acid constructs containing hybrid promoters for use in gene therapy and genetic manipulation. The invention relates to a nucleic acid construct for the precise, regulated expression of genes in host cells, which construct exhibits at least one mutation which inhibits the proper expression of the expressed gene and exhibits at least one additional second mutation which relieves the inhibition due to the first mutation, to an isolated cell which harbors the nucleic acid construct, and to the use of the nucleic acid construct for preparing pharmaceuticals and for treating diseases with excessive cell proliferation.

17 Claims, 15 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

---------- KWIC ---------

Brief Summary Text - BSTX (31):

The promoter sequence, enhancer sequence or activator sequence can be selected from the group of gene-regulatory nucleotide sequences which activate in endothelial cells, smooth muscle cells, striated muscle cells, macrophages,

lymphocytes, tumor cells, liver cells, leukemia cells and glia cells, or of promoter sequences from the **HBV,** HCV, HSV, HPV, EBV, HTLV or HIV viruses.

Detailed Description Text - DETX (9):

Particular preference is given to the following promoter or enhancer sequences: those promoter sequences or enhancer sequences which activate transcription cell-specifically in endothelial cells, smooth muscle cells, striated muscle cells, hematopoietic cells, lymphocytes, macrophages, glia cells or tumor cells; and/or promoter sequences or enhancer sequences of the **HBV,** HCV, HSV, HPV, CMV, EBV, HTLV or HIV viruses; and/or promoter sequences or enhancer sequences which can be metabolically activated, such as the hypoxia-inducible enhancer (Semenza et al., PNAS 88, 5680 (1991)) or promoter (Mc Burney et al., Nucleic Acids Res. 19, 5755 (1991); WO 95/21927); and/or promoters which can be activated cell cycle-specifically, such as the promoter of the cdc25C gene, of the cyclin A gene, of the cdc2 gene (Lucibello et al., EMBO J. 14, 132 (1995), Zwicker et al., EMBO J. 14, 4514 (1995), Zwicker et al., Nucl. Acids Res. 23, 2833 (1995)), of the B-myb gene (Lam et al., EMBO J. 12, 2705 (1993)), of the DHFR gene (Means et al., Mol. Cell Biol. 12, 1054 (1992)) and of the E2F-1 gene (Johnson et al., Genes Dev. 8, 1514 (1994), Hsiao et al., Genes Dev. 8, 15256 (1994)) or else sequences for binding transcription factors which appear or are activated during cell proliferation. Examples of these binding sequences are monomers or multimers of the nucleotide sequence termed the Myc E box (Blackwood and Eisenmann, Science 251, 1211 (1991)).

Detailed Description Text - DETX (30):

The NRS (component (h)) is preferably the retroviral rev-responsive element (RRE) sequence. In the case of HIV-1, this RRE is a sequence encompassing 243 nucleotides (nucleotides 7362-7595; Muesing et al., Nature 313, 450 (1985)) in the env gene (Malim et al., Nature 338, 254 (1989); Kjems et al., PNAS 88, 683 (1991)). However, within the meaning of the invention, the nuclear retention signal (NRS) can also be any homologous and/or functionally similar (analogous) nucleotide sequence, such as, for example, the RRE-equivalent element in the **HBV** virus (Huang et al., Mol Cell Biol. 13, 7476 (1993)).

Detailed Description Text - DETX (114):

Examples of these viruses are **HBV,** HCV, HSV, HPV, HIV, EBV and HTLV.

Detailed Description Text - DETX (123):

The active substance to be selected is the DNA for either an antibody or an antibody fragment which is specific for the infective agent, or the DNA for a protein which is formed by the infective agent and which leads, by means of triggering an immune reaction, i.e. due to antibody binding and/or due to cytotoxic T lymphocytes, to the neutralization and/or destruction of the agent. So-called neutralization antigens of this nature are already employed as vaccine antigens (see review in Ellis, Adv. Exp. Med. Biol. 327, 263 (1992)). Examples of DNA sequences which encode neutralization antigens can be obtained from the following publications: Influenza A virus antigen (Ulmer et al., Science 259, 1745 (1993), Robinson et al., Vaccine 11, 957 (1993), Fynan

et al., Int. J. Immunopharmac. 17, 79 (1995)) HIV antigens (Wang et al., PNAS USA 90, 4156 (1993)) Rabies virus antigen (Donnelly et al., Immunol. 2/1, 20 (1994)) HSV (herpes simplex virus) antigen (Fleckenstein et al., Nature 274, 57 (1978)) RSV (respiratory syncytial virus) antigen (Du et al., Bio/Tech. 12, 813 (1994), Hall, Science 265, 1393 (1993)) Parainfluenza virus antigen (Du et al., Bio/Techn. 12, 813 (1994)) Rotavirus antigen (Albert et al., J. Clin. Microbiol. 25, 183 (1987), Anderson et al., J. Infect. Dis. 153, 823 (1986), Battaglia et al., J. Infect. Dis. 155, 140 (1987), Chanock et al., J. Infect. Dis. 148, 49 (1983), Dyall-Smith et al., J. Virol. 38, 1099 (1981), Glass et al., Science 265, 1389 (1994)) VZV (varicella zoster virus) antigen (Straus et al., Ann. Intern. Med. 109, 438 (1988), Gershon, Pediatr. Infect. Dis. 2, 171 (1991), Kinchington et al., J. Virol. 64, 4540 (1990)) CMV (cytomegalovirus) antigen (Plotkin, Science 265, 1383 (1994)) Measles virus antigen (Katz and Kellin, Science 265, 1391 (1994)) HPV (human papillomvirus) antigen (Tindl and Frazer, Curr. Topics Microbiol. Immunol. 186, 217 (1994)) **HBV** (hepatitis B virus) antigen (Valenzuela et al., Nature 280, 815 (1979), Heerman et al., J. Virol. 52, 396 (1984)) HCV (hepatitis C virus) antigen (Cerny et al., Curr. Topics Microbiol. Immunol. 189, 169 (1994), Esteban et al., Progr. Liver Dis. 10, 253 (1992), Jung et al., Eur. J. Clin. Invest. 24, 641 (1994)) HDV (hepatitis D virus) antigen (Iwarson, Scand. J. Infect. Dis. 24, 129 (1992), Consolo et al., Nephron. 61, 251 (1992)) HEV (hepatitis E virus) antigen (Iwarson, Scand. J. Infect. Dis. 24, 129 (1992), Consolo et al., Nephron. 61, 251 (1992)) HAV (hepatitis A virus) antigen (d'Hondt, Vaccine 10, 48 (1992), Andre, J. Infect. Dis. 171, 33 (1995), Lemon et al., Vaccine 10, 40 (1992), Melnick et al., Vaccine 10, 24 (1992), Flehmig, Baillieres Clin. Gastroenterol. 4, 707 (1990)) Vibrio cholera antigen (Levine and Kaper, Vaccine 11, 207 (1993)) Borrelia burgdorferi antigen (Schaible et al., Immunol. Letters 36, 219 (1993), Wallich et al., Lab. Med. 17, 669 (1993)) Helicobacter pylori antigen (Crabtree et al., Lancet 338, 332 (1991), Blaser, J. Infect. Dis. 161, 626 (1990), Cover and Blaser, J. Biol. Chem. 267, 10570 (1993), Cover et al., Infect. Immunol. 58, 603 (1990), Dunn et al., J. Biol. Chem. 265, 9464 (1990), Dunn et al., Infect. Immunol. 60, 1946 (1992), Lage et al., Acta Gastroenterol. Belg. 56 (suppl.), 61 (1993), Mobley et al., Scand. J. Gastroint. 26 (suppl. 187), 39 (1991)) Malaria antigen (Nussenzweig and Long, Science 265, 1381 (1994), Maurice, Science 267, 320 (1995), Enders et al., Vaccines 10, 920 (1992), Knapp et al., Infect. Imm. 60, 2397 (1992))

Claims Text - CLTX (4):

4. The nucleic acid construct of claim 2, wherein the nucleic acid sequence encoding the NRS is selected from the group consisting of the Rev-responsive element (RRE) from HIV-1 or HIV-2, the RRE-equivalent retention signal from retroviruses other than HIV-1 and HIV-2, and the RRE-equivalent retention signal from **HBV**.

Other Reference Publication - OREF (120):

Huang, J., et al., "A Novel Hepatitis B Virus (**HBV**) Genetic Element with Rev Response Element-Like Properties That Is Essential for Expression of **HBV** Gene Products", Molecular and Cellular Biology, vol. 13, pp. 7476-7486 (1993).

Other Reference Publication - OREF (177):

Mukhopadhyay, et al., "Hypoxic induction of human vascular endothelial growth factor expression through c-**Src activationp**", Nature, vol. 375, pp. 577-581 (1995).

US-PAT-NO: 6503914

DOCUMENT-IDENTIFIER: US 6503914 B1
See image for Certificate of Correction

TITLE: Thienopyrimidine-based inhibitors of the Src family

DATE-ISSUED: January 7, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Benish; Michele A.	Pearland	TX	N/A	N/A
Lawless; Michael	St. Charles	MO	N/A	N/A
Budde; Raymond J. A.	Bellaire	TX	N/A	N/A

APPL-NO: 09/ 694145

DATE FILED: October 23, 2000

US-CL-CURRENT: 514/260.1, 544/278

ABSTRACT:

Various thienopyrimidine-based analog compounds that selectively inhibit the Src family of tyrosine kinases. These compounds are thienopyrimidines and contain a hydrozone bridge created by heating a thienopyrimidine hydrazine with an aldehyde in ethanol at reflux. Such compounds are useful in the treatment of various diseases including hyperproliferative diseases, hematologic diseases, osteoporosis, neurological diseases, autoimmune diseases, allergic/immunological diseases, or viral infections.

99 Claims, 6 Drawing figures

Exemplary Claim Number: 1

Number of Drawing Sheets: 6

---------- KWIC ---------

Brief Summary Text - BSTX (7):

Src activity is greatly increased in many human cancers: breast cancer (Ottenhoff-Kalff et al., 1992; Partanen, 1994), stomach cancer (Takeshima et al., 1991), colon cancer (Rosen et al., 1986; Bolen et al., 1985; Bolen et al., 1987; Cartwright et al., 1989; Cartwright et al., 1990; Talamonti et al., 1992; Talamonti et al., 1993; Termuhlen et al., 1993), hairy cell leukemia and a subgroup of B-cell lymphomas (Lynch et al., 1993), low grade human bladder carcinoma (Fanning et al., 1992), neuroblastoma (Bolen et al., 1985; O'Shaughnessy et al., 1987; Bjelfman et al., 1990), ovarian cancer (Wiener et

al., 1999) and non-small cell lung carcinoma (Budde et al., 1994). In the case of colon cancer, **Src is activated** more frequently than Ras or p53 (Jessup and Gallick, 1993), and undergoes two distinct activations corresponding with malignant transformation of colonocytes (Cartwright et al., 1990) and tumor progression (Talamonti et al., 1991, 1992; Termuhlen et al., 1993). Antisense to Src inhibits growth of human monoblastoid leukemia cells (Waki et al., 1994), K562 human leukemia cells (Kitanaka et al., 1994) and HT-29 human colon cancer cells (Staley et al., 1995). In addition, growth inhibition of colon tumor (Garcia et al., 1991; Novotny-Smith & Gallick, 1992) and neuroblastoma cell lines (Preis et al., 1988) correlate with decreases in tyrosine kinase activity of Src. In a colon adenocarcinoma cell line, HT29, the mRNA expression of vascular endothelial growth factor (VEGF) was decreased in proportion to the decrease in Src kinase activity caused by expression of a Src antisense expression vector. In nude mice, there was a decrease in tumor vascularity in subcutaneous tumors from Src antisense transfectants (Ellis et al., 1998). Src activity was reduced in a human ovarian cancer cell line (SKOv-3) by antisense technology. The reduced Src activity in SKOv-3 was associated with altered cellular morphology, reduced anchorage-independent growth, diminished tumor growth and reduced vascular endothelial growth factor mRNA expression in vitro (Wiener et al., 1999).

Brief Summary Text - BSTX (12):

Herpesviridae, papovaviridae, and retroviridae have been shown to interact with non-receptor tyrosine kinases and use them as signaling intermediates. The HIV-1 Nef protein interacts with members of the Src family of tyrosine kinases. Nef mediates downregulation of CD4 membrane expression, modification of T-cell activation pathways, and increases virus infectivity (Collette et al., 1997). The **HBx** protein of the hepatitis B virus is essential for infection by hepadnaviruses and **activates Ras by activating the Src** family of tyrosine kinases. The activation of Ras is necessary for the ability of the **HBx** protein to stimulate transcription and release growth arrest in quiescent cells (Klein and Schneider, 1997). Activity of the Src family of tyrosine kinases is altered by association with viral proteins such as mouse and hamster polyomavirus middle-T antigens, Epstein-Barr virus LMP2A, and herpesvirus saimiri Tip (Dunant and Ballmer-Hofer, 1997).

Detailed Description Text - DETX (205):

Bolen J B, Veillette A, Schwartz A M, Deseau V, Rosen N: **Activation of pp60c-src** in human colon carcinoma and normal human colon mucosal cells. Oncogene Res 1:149-168, 1987.

Detailed Description Text - DETX (206):

Bolen J B, Veillette A, Schwartz A M, Deseau V, Rosen N: **Activation of pp60c-src** protein kinase activity in human colon carcinoma. Proc Natl Acad Sci USA 84:2251-2255, 1987.

Detailed Description Text - DETX (216):

Cartwright C A, Kamps M P, Meisler A I, Pipas J M, Eckhart W: p60c-**src**

activation in human colon carcinoma. J Clin Invest 83:2025-2033, 1989.

Detailed Description Text - DETX (217):
Cartwright C A, Meisler A I, Eckhart W: **Activation of the pp60c-src** protein kinase is an early event in colonic carcinogenesis. Proc Natl Acad Sci USA 87:558-562, 1990.

Detailed Description Text - DETX (219):
Chackalaparampil I, Shalloway D: Altered phosphorylation and **activation of pp60c-src** during fibroblast mitosis. Cell 52:801-810, 1988.

Detailed Description Text - DETX (255):
Klein N P and Schneider R J. **Activation of Src** Family Kinases by Hepatitis B Virus **HBx** Protein and Coupled Signaling to Ras. Mol Cell Biol 17:6427-6436, 1997.

Detailed Description Text - DETX (281):
Sabe H, Okada M, Nakagawa H, Hanafusa H: **Activation of c-src** in cells bearing v-Crk and its suppression by C S K. Mol. Cell Biol. 12:4706-4713, 1992.

Detailed Description Text - DETX (313):
Zheng X M, Wang Y, and Pallen C J: Cell transformation and **activation of pp60c-src** by overexpression of a protein tyrosine phosphatase. Nature 359:336-339, 1992.

	L #	Hits	Search Text	DBs	Time Stamp
1	L1	116	hbx	USPAT; US-PGPUB	2003/07/08 09:44
2	L2	362	(hepatitis adj b adj virus or hbv) near4 inhibit$8	USPAT; US-PGPUB	2003/07/08 09:45
3	L3	15	1 and 2	USPAT; US-PGPUB	2003/07/08 09:45
4	L4	6	hbx near4 inhibit$8	USPAT; US-PGPUB	2003/07/08 10:44
5	L5	7091	src	USPAT; US-PGPUB	2003/07/08 10:46
6	L6	665867	activat$8	USPAT; US-PGPUB	2003/07/08 10:46
7	L7	201531	upstream	USPAT; US-PGPUB	2003/07/08 10:47
8	L8	2769	6 near5 7	USPAT; US-PGPUB	2003/07/08 10:47
9	L9	19	8 same 5	USPAT; US-PGPUB	2003/07/08 10:47
10	L10	61	5 same 6 same 7	USPAT; US-PGPUB	2003/07/08 10:53
11	L11	221	5 near2 (activator$1 or activation)	USPAT; US-PGPUB	2003/07/08 11:17
12	L12	2937	hbv or hbx	USPAT; US-PGPUB	2003/07/08 11:17
13	L13	9	11 and 12	USPAT; US-PGPUB	2003/07/08 11:18
14	L14	529	5 near5 6	USPAT; US-PGPUB	2003/07/08 11:38
15	L15	29	12 and 14	USPAT; US-PGPUB	2003/07/08 11:38
16	L16	8317	cyclosporin or csa	USPAT; US-PGPUB	2003/07/08 12:10
17	L17	182	16 and 12	USPAT; US-PGPUB	2003/07/08 12:10
18	L18	1	16 same 12	USPAT; US-PGPUB	2003/07/08 12:10

PGPUB-DOCUMENT-NUMBER: 20020045191

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020045191 A1

TITLE: Inhibition of the SRC kinase family pathway as a method of treating HBV infection and hepatocellular carcinoma

PUBLICATION-DATE: April 18, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Schneider, Robert J.	New York	NY	US	
Klein, Nicola	Palo Alto	CA	US	

APPL-NO: 09/ 955006

DATE FILED: September 17, 2001

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60232892 20000915 US

US-CL-CURRENT: 435/7.1, 435/15 , 514/262.1 , 514/44 , 514/520 , 514/7 , 536/24.5

ABSTRACT:

The present invention relates to therapeutic protocols and pharmaceutical compositions designed to target HBx mediated activation of Src kinase, members of the Src tyrosine kinase family and components of the Src kinase family signal transduction pathways for the treatment of HBV infection and related disorders and diseases, such as HCC. The invention further relates to pharmaceutical compositions for the treatment of HBV infection targeted to HBx and its essential activities required to sustain HBV replication. The invention is based, in part, on the Applicants' discovery that activation of Src kinase signaling cascades play a fundamental role in mammalian hepadnavirus replication. Applicants have demonstrated that HBx mediates activation of the Src family of kinases and that this activation is a critical function provided by HBx for mammalian hepadnavirus replication.

---------- KWIC ---------

Summary of Invention Paragraph - BSTX (18):

[0015] The Applicants have shown that **HBx** activation of Src kinases stimulates viral DNA replication; and **HBx** activates Src kinases by stimulating two related upstream tyrosine kinases known as Pyk2 and p125FAK (FAK). The Applicants have shown that **HBx** activation of Pyk2, FAK, Src and MAPK

signalling, all occur in a calcium-dependent manner in that treatment of cells with calcium chelator (EGTA) or calcium channel poison (BAPTA-AM) specifically blocks **HBx** stimulation of Pyk2, which is essential for **HBx** activity. In addition, treatment of cells with **cyclosporin** A (**CsA**), a specific inhibitor of mitochondrial voltage-dependent anion channels, which deregulates calcium channels, also impairs **HBx** stimulation of **HBV** genomic DNA replication. Thus, the Applicants have demonstrated that **HBx** functions through a calcium-dependent pathway to stimulate viral DNA replication in cells and Pyk2 signal transduction, which plays a fundamental role in mammalian hepadnavirus replication.

Brief Description of Drawings Paragraph - DRTX (20):

[0049] TPA treatment was for 20 mm using 20 ng/ml. (B) Chang cells treated 2 h with 50 .mu.M BAPTA-AM, 4 h with 3 .mu.M **CsA**, or 2 h with 0.5 mM EGTA were analyzed by immunoblot as above. (C) Chang cells transfected with vector or pAdCMVX were treated 2h with 0.5 mM or 3 mM EGTA, and Pyk2 examined by immunoblot. (D) HepG2 cells were transfected with **HBV**, **HBx(-) HBV** genomic DNA or vector, complemented by 2 .mu.g plasmid pAdCMVX. Cytoplasmic **HBV** core particles were isolated from equal numbers of cells (Klein, et al. 1997, EMBOJ 18: 5019-5027) and viral DNA replication intermediates detected by Southern blot as described (Klein, et al. 1997, EMBOJ 18: 5019-5027). The smear represents 4 kb (mature double-stranded DNA) to 2 kb (first-strand single-stranded DNA). Northern blot analysis was carried out using poly(A+) RNA extracted from equal numbers of cells. (E) Southern and Northern blot analyses were performed on HepG2 cells transfected as above with or without pPKM or PPRKS. Typical experiments are shown.

Brief Description of Drawings Paragraph - DRTX (21):

[0050] FIG. 10. HepG2 cells were transfected as in FIG. 8 legend, allowed to recover and treated for 4 d with (A) 1 .mu.g/ml or 3 .mu.g/ml **CsA**, or (C) 2.5 .mu.M or 25 .mu.M BAPTA-AM. Cytoplasmic viral core particles were isolated and **HBV** DNA replication and mRNA levels detected by Southern and Northern blot hybridization. (D) HepG2 cells were transfected with ABS or AdCMVX (**HBx**) plasmids and luciferase reporters containing 4 binding sites for AP-1 or CREB, linked to a TATA box promoter. Cells were treated with **CsA** as above and assayed for luciferase activity. (B) Endogenous polymerase activity of **HBV** pol protein was assayed in isolated cytoplasmic core particles obtained as above, using [.alpha.-.sup.32P]-dNTPs in vitro as described (Nassal, 1992, J. Virol. 66: 4107-4116). Products were resolved by electrophoresis and detected by autoradiography. Typical results are shown.

Detail Description Paragraph - DETX (12):

[0062] Applicants have demonstrated that **HBx** activation of Pyk2, FAK, Src and MAPK signaling all occur in a calcium-dependent manner in that treatment of cells with a calcium chelator (EGTA) or calcium channel poison (BAPTA-AM) specifically blocks **HBx** stimulation of Pyk2, which is essential for **HBx** activity. Overexpression of dominant-interfering forms of Pyk2 or FAK also block **HBx** transactivation activity. Further, Applicants have shown that the treatment of cells with **cyclosporin** A (**CSA**), a specific inhibitor of

mitochondrial voltage-dependent anion channels, which deregulates calcium channels, also impairs **HBx** stimulation of **HBV** genomic DNA replication.

Detail Description Paragraph - DETX (190):

[0228] Studies determined whether **HBx** acts on intracellular calcium to activate Pyk2. **HBx** transfected Chang cells showed 5 fold increased phosphorylation of Pyk2 at Y-402, similar to TPA stimulation (FIG. 9A). Treatment with the cell permeable cytosolic calcium chelator BABTA-AM at 50 .mu.M (2 times IC.sub.50) for 2 h prevented Pyk2 phosphorylation without altering Pyk2 levels (FIG. 9A). **HBx** activation of Pyk2 therefore involves cytosolic calcium action. Studies next determined whether **HBx** acts on calcium channels in the endoplasmic reticulum (ER), mitochondria or plasma membrane (PM) for its activity. A low (0.5 mM) concentration of EGTA was added to the culture medium for 2 h to block entrance of extracellular calcium (Zwick et al. 1999, J.B.C. 274: 20989-20996), or cells were treated with BAPTA-AM to block ER and mitochondrial calcium, or **cyclosporin** A (**CsA**) to block mitochondrial calcium function. EGTA had no effect whereas BAPTA-AM or GsA both prevented **HBx** activation of Pyk2, indicating that **HBx** acts on ERimitochondrial calcium control. A high concentration of EGTA (3 mM) did not block TPA activation of Pyk2 phosphorylation (Zwick et al. 1999, J.B.C. 274: 20989-20996) (FIG. 9C), but partially inhibited activation by **HBx**. Therefore, **HBx** acts on the control of ER/mitochondrial calcium, with low level entry of extracellular calcium, suggestive of constitutive cytosolic calcium alteration (Clapham 1997, Cell 80:259-268).

Detail Description Paragraph - DETX (192):

[0230] The requirement for cytosolic calcium in **HBx**-dependent viral replication was investigated. Cells transfected with wild type or **HBx(-) HBV** genomic DNA were treated for 4 d with 1 or 3 p.g/ml of **CsA** to block mitochondrial calcium channels. There was no evidence for **CsA** toxicity during treatment. **CsA** reduced **HBV** DNA replication in cytoplasmic core particles by 15 fold compared to untreated controls (FIG. 10A), similar in magnitude to inhibition of Pyk2 or the absence of **HBx** expression. Northern mRNA analysis demonstrated a 2 fold reduction in pgRLNA and HBsAg mRNAs (FIG. 10A). To determine whether inhibiting cytosolic calcium and Pyk2 activity inhibits **HBV** DNA replication, HepG2 cells were transfected with **HBV** genomic DNA and treated with **CsA**, or cotransfected with PKM. Cytosolic core particles were purified and incubated with [.alpha.-.sup.32P]-dNTPs to examine endogenous **HBV** polymerase activity (FIG. 10B). In untreated controls, predominantly full-length double-strand DNA products were produced, indicative of pgRNA reverse transcription and DNA-dependent DNA synthesis. PKM inhibition of Pyk2 or treatment of cells with **CsA** prevented DNA replication by 7 and 12 fold respectively. Treatment of **HBV** genome transfected cells with low levels of BAPTA-AM for 4 d impaired viral DNA replication by 10 fold without strongly reducing **HBV** mRNA levels (FIG. 10C). Collectively, these data show that **HBx** activation of **HBV** reverse transcription and DNA replication involves alteration of cytosolic calcium and coupled activation of Pyk2. The requirement for cytosolic calcium in **HBx** transcriptional stimulation was investigated in HepG2 cells transfected with luciferase reporters controlled by transcription factor AP- 1or CREB, with or without treatment of cells by **CsA** (FIG. 10D). **HBx**

activation of AP- 1 dependent transcription was impaired 2.5 fold by treatment of cells with 10 .mu.g/ml **CsA**. **HBx** stimulation of CREB-dependent transcription was resistant to high dose **CsA** treatment, consistent with **HBx** activation of CREB by direct interaction (Andrisani et al., 1999, J. Oncol. 15: 1-7). These data indicate that **HBx** transcriptional activation of AP- 1 but not CREB requires alteration of cytosolic calcium.

Detail Description Paragraph - DETX (194):

[0232] In summary, a major finding of this work is that **HBx** acts on cytosolic stored calcium to stimulate Pyk2-Src kinase signal transduction pathways that activate **HBV** reverse transcription and DNA replication, and in some instances, to function as a moderate transcriptional activator. Three lines of evidence indicate that **HBx** stimulation of **HBV** reverse transcription/DNA replication involves alteration of cytosolic calcium and activation of Pyk2-Src kinase signal transduction. First, activation of Pyk2, which is critical for stimulation of **HBV** DNA replication in tissue culture, is typically mediated by increased levels of cytosolic calcium. Chelation of cytosolic calcium with BAPTA-AM blocked **HBx** activation of Pyk2 and **HBV** DNA replication. Second, inhibition of mitochondrial and possibly ER calcium channels with **CsA** blocked **HBx** activation of **HBV** DNA replication. Third, ionophoric agents that increase the level of cytoplasmic calcium functionally replace **HBx** in viral DNA replication. Thus, **HBx** acts on stored cytosolic calcium as a fundamental activity for **HBV** replication.

	L #	Hits	Search Text	DBs	Time Stamp
1	L1	116	hbx	USPAT; US-PGPUB	2003/07/08 09:44
2	L2	362	(hepatitis adj b adj virus or hbv) near4 inhibit$8	USPAT; US-PGPUB	2003/07/08 09:45
3	L3	15	1 and 2	USPAT; US-PGPUB	2003/07/08 09:45
4	L4	6	hbx near4 inhibit$8	USPAT; US-PGPUB	2003/07/08 10:44
5	L5	7091	src	USPAT; US-PGPUB	2003/07/08 10:46
6	L6	665867	activat$8	USPAT; US-PGPUB	2003/07/08 10:46
7	L7	201531	upstream	USPAT; US-PGPUB	2003/07/08 10:47
8	L8	2769	6 near5 7	USPAT; US-PGPUB	2003/07/08 10:47
9	L9	19	8 same 5	USPAT; US-PGPUB	2003/07/08 10:47
10	L10	61	5 same 6 same 7	USPAT; US-PGPUB	2003/07/08 10:53
11	L11	221	5 near2 (activator$1 or activation)	USPAT; US-PGPUB	2003/07/08 11:17
12	L12	2937	hbv or hbx	USPAT; US-PGPUB	2003/07/08 11:17
13	L13	9	11 and 12	USPAT; US-PGPUB	2003/07/08 11:18
14	L14	529	5 near5 6	USPAT; US-PGPUB	2003/07/08 11:38
15	L15	29	12 and 14	USPAT; US-PGPUB	2003/07/08 11:38
16	L16	8317	cyclosporin or csa	USPAT; US-PGPUB	2003/07/08 12:10
17	L17	182	16 and 12	USPAT; US-PGPUB	2003/07/08 12:13
18	L18	1	16 same 12	USPAT; US-PGPUB	2003/07/08 12:10
19	L19	304	bapta or cgp37157	USPAT; US-PGPUB	2003/07/08 12:13
20	L20	5	19 and 12	USPAT; US-PGPUB	2003/07/08 12:13

PGPUB-DOCUMENT-NUMBER: 20030119029

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20030119029 A1

TITLE: Compositions and methods relating to novel benzodiazepine compounds and targets thereof

PUBLICATION-DATE: June 26, 2003

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Glick, Gary D.	Ann Arbor	MI	US	
Opipari, Anthony W.	Ann Arbor	MI	US	

APPL-NO: 10/ 217878

DATE FILED: August 13, 2002

RELATED-US-APPL-DATA:

child 10217878 A1 20020813

parent continuation-in-part-of 09767283 20010122 US PENDING

child 09767283 20010122 US

parent continuation-of 09700101 20001108 US PENDING

child 09700101 20001108 US

parent a-371-of-international PCT/US00/11599 20000427 WO PENDING

non-provisional-of-provisional 60131761 19990430 US

non-provisional-of-provisional 60165511 19991115 US

non-provisional-of-provisional 60191855 20000324 US

non-provisional-of-provisional 60312560 20010815 US

non-provisional-of-provisional 60313689 20010820 US

US-CL-CURRENT: 435/6, 435/235.1 , 435/325 , 514/221

ABSTRACT:

The present invention relates to novel chemical compounds, methods for their discovery, and their therapeutic use. In particular, the present invention provides benzodiazepine derivatives and methods of using benzodiazepine

derivatives as therapeutic agents to treat a number of conditions associated with the faulty regulation of the processes of programmed cell death, autoimmunity, inflammation, and hyperproliferation, and the like.

[0001] This application is a Continuation in Part of U.S. patent application Ser. No. 09/767,283, filed Jan. 22, 2001, which is a continuation of U.S. patent application Ser. No. 09/700,101, filed Nov. 8, 2000, which is the National entry of PCTUS00/11599 filed Apr. 27, 2000, which claims priority to U.S. Provisional Application Serial No. 60/131,761, filed Apr. 30, 1999, to U.S. Provisional Application Serial No. 60/165,511, filed Nov. 15, 1999, and to U.S. Provisional Application Serial No. 60/191,855, filed Mar. 24, 2000. This application also claims priority to U.S. Provisional Application Serial No. 60/312,560, filed Aug. 15, 2001, to U.S. Provisional Application Serial No. 60/313,689, filed Aug. 20, 2001, and to U.S. Provisional Application Express Mail No.: EV092300423, filed Jul. 18, 2002. Each aforementioned application is specifically incorporated herein by reference in it entirety.

---------- KWIC ---------

Detail Description Paragraph - DETX (112):
[0153] The human viruses of non-herpes origin include, but are not limited to, influenza viruses A, B and C; parainfluenza viruses-1,2, 3 and 4; adenovirus; reovirus; respiratory syncytial virus; rhinovirus; coxsackle virus; echo virus; rubeola virus; hepatitis viruses of the types Band C (**HBV** and HCV); and papovavirus.

Detail Description Paragraph - DETX (155):
[0196] The dependence of sensitized death on pro-apoptotic signals that function in B cells was also tested. Chelating extracellular calcium with 1,2-bis(2-aminophenoxy)ethane-N,N,N',N'-tetraaceticacid (**BAPTA**) minimally reduced non-sensitized death while substantially protecting sensitized cells (7% vs. 71% inhibition, respectively). The effect of **BAPTA** is unrelated to its ability to blunt the rapid BCR-induced calcium flux because it is protective even when added 1 hour after stimulation. Inhibition of caspase activity with z-VAD (un-activated: 31% vs. activated: 86%), the mitochondrial permeability transition (MPT) with cyclosporin (CsA) (un-activated: 9% vs. activated: 54%) and protein synthesis with cyclohexamide (un-activated: 19% vs. activated: 64%) only protected sensitized cells. Inhibiting calcineurin (with FK506 10 nM) was not protective in either condition. The antioxidants vitamin E and superoxide (O.sub.2.sup.-)-specific MnTBAP each protected activated and unactivated cells to a similar extent (.about.80%) suggesting that O.sub.2.sup.- is an essential event in Bz-423-induced signaling. These experiments show that high concentrations of Bz-423 generates superoxide which kills cells independently of these other mediators of apoptosis.

Detail Description Paragraph - DETX (156):
[0197] O.sub.2.sup.- in activated and un-activated cells using hydroethidium which is a selective indicator of O.sub.2.sup.-, was also measured. O.sub.2.sup.- increases in both un-activated and activated cells within 1 hour

of exposure to Bz-423 (FIG. 4A) which is prior to the MPT. MnTBAP and vitamin E reduced O.sub.2.sup.- levels, but z-VAD, **BAPTA** and CsA did not. The amount of O.sub.2.sup.- increases with increasing concentration of Bz-423, and in the absence of BCR stimulation, correlates with cell death measured at 24 h. However, for a given concentration of Bz-423, BCR stimulation does not increase O.sub.2.sup.- relative to un-activated cells (FIGS. 4A-4C). Hence, the role of superoxide in cell death differs in activated cells. BCR activated cells are killed by lower concentration of Bz-423 through a mechanism in which BCR cross-linking sensitizes cells to O.sub.2.sup.-, gene expression, caspase, and mitochondria-dependent processes to occur.

PGPUB-DOCUMENT-NUMBER: 20020187498

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020187498 A1

TITLE: Skin substitutes for irritancy testing

PUBLICATION-DATE: December 12, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Comer, Allen	Madison	WI	US	
Allen-Hoffmann, Lynn	Madison	WI	US	
Hoffmann, Michael	Madison	WI	US	

APPL-NO: 10/ 087388

DATE FILED: March 1, 2002

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60287898 20010501 US

non-provisional-of-provisional 60273034 20010302 US

US-CL-CURRENT: 435/6, 435/371

ABSTRACT:

The present invention relates to in vitro cultured skin substitutes, preferably to in vitro cultured skin substitutes that have improved barrier function. In particular, the present invention relates to the use of such skin substitutes for irritancy testing. The present invention provides improved methods of screening compounds for irritancy activity, as well for identifying novel irritant responsive genes.

[0001] This application claims priority to U.S. provisional patent applications serial Nos. 60/287,898, filed May 1, 2001 and 60/273,034, filed Mar. 2, 2001. This patent application was supported in part by NIH SBIR grant 1 R43 ES010692-01A1. The government has certain rights in the invention.

---------- KWIC ---------

Detail Description Paragraph - DETX (63):

[0074] The NIKS cells arose from the BC-1-Ep strain of human neonatal foreskin keratinocytes isolated from an apparently normal male infant. In early passages, the BC-1-Ep cells exhibited no morphological or growth characteristics that were atypical for cultured normal human keratinocytes.

Cultivated BC-1-Ep cells exhibited stratification as well as features of programmed cell death. To determine replicative lifespan, the BC-1-Ep cells were serially cultivated to senescence in standard keratinocyte growth medium at a density of 3.times.10.sup.5 cells per 100-mm dish and passaged at weekly intervals (approximately a 1:25 split). By passage 15, most keratinocytes in the population appeared senescent as judged by the presence of numerous abortive colonies which exhibited large, flat cells. However, at passage 16, keratinocytes exhibiting a small cell size were evident. By passage 17, only the small-sized keratinocytes were present in the culture and no large, senescent keratinocytes were evident. The resulting population of small keratinocytes that survived this putative crisis period appeared morphologically uniform and produced colonies of keratinocytes exhibiting typical keratinocyte characteristics including cell-cell adhesion and apparent squame production. The keratinocytes that survived senescence were serially cultivated at a density of 3.times.10.sup.5 cells per 100-mm dish. Typically the cultures reached a cell density of approximately 8.times.10.sup.6 cells within 7 days. This stable rate of cell growth was maintained through at least 59 passages, demonstrating that the cells had achieved immortality. The keratinocytes that emerged from the original senescencing population were originally designated BC-1-Ep/Spontaneous Line and are now termed NIKS. The NIKS cell line has been screened for the presence of proviral DNA sequences for HIV-1, HIV-2, EBV, CMV, HTLV-1, HTLV-2, **HBV,** HCV, B-19 parvovirus, HPV-16 and HPV-31 using either PCR or Southern analysis. None of these viruses were detected.

Detail Description Paragraph - DETX (97):

[0108] In some embodiments, the second messenger assays measure fluorescent signals from reporter molecules that respond to intracellular changes (e.g., Ca.sup.2+ concentration, membrane potential, pH, IP3, cAMP, arachidonic acid release) due to stimulation of membrane receptors and ion channels (e.g., ligand gated ion channels) (Denyer et al., Drug Discov. Today 3:323-32 (1998); Gonzales et al., Drug. Discov. Today 4:431-39 (1999)). Examples of reporter molecules include, but are not limited to, florescence resonance energy transfer systems (e.g., Cuo-lipids and oxonols, EDAN/DABCYL), calcium sensitive indicators (e.g., Fluo-3, FURA 2, INDO 1, and FLUO3/AM, **BAPTA** AM), chloride-sensitive indicators (e.g., SPQ, SPA), potassium-sensitive indicators (e.g., PBFI), sodium-sensitive indicators (e.g., SBFI), and pH sensitive indicators (e.g., BCECF).

PGPUB-DOCUMENT-NUMBER: 20020168768

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020168768 A1

TITLE: Skin substitutes with improved barrier function

PUBLICATION-DATE: November 14, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Comer, Allen	Madison	WI	US	
Allen-Hoffmann, Lynn	Madison	WI	US	
Hoffmann, Michael	Madison	WI	US	

APPL-NO: 10/ 087346

DATE FILED: March 1, 2002

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60273034 20010302 US

US-CL-CURRENT: 435/371, 424/93.7

ABSTRACT:

The present invention relates to in vitro cultured skin substitutes, and in particular to in vitro cultured skin substitutes that have improved barrier function. In some embodiments, improved barrier function is a result of improved culture conditions, while in other embodiments, improved barrier function results from genetic modification of keratinocytes. Improved culture conditions to improve barrier function include organotypic culture in the presence of linoleic acid and/or linoleic acid at about 75% humidity. Suitable genetic modifications for improving barrier function includes transfection with a DNA construct capable of expressing GKLF.

---------- KWIC ---------

Detail Description Paragraph - DETX (59):

[0072] The NIKS cells arose from the BC-1-Ep strain of human neonatal foreskin keratinocytes isolated from an apparently normal male infant. In early passages, the BC-1-Ep cells exhibited no morphological or growth characteristics that were atypical for cultured normal human keratinocytes. Cultivated BC-1-Ep cells exhibited stratification as well as features of programmed cell death. To determine replicative lifespan, the BC-1-Ep cells were serially cultivated to senescence in standard keratinocyte growth medium at a density of 3.times.10.sup.5 cells per 100-mm dish and passaged at weekly

intervals (approximately a 1:25 split). By passage 15, most keratinocytes in the population appeared senescent as judged by the presence of numerous abortive colonies which exhibited large, flat cells. However, at passage 16, keratinocytes exhibiting a small cell size were evident. By passage 17, only the small-sized keratinocytes were present in the culture and no large, senescent keratinocytes were evident. The resulting population of small keratinocytes that survived this putative crisis period appeared morphologically uniform and produced colonies of keratinocytes exhibiting typical keratinocyte characteristics including cell-cell adhesion and apparent squame production. The keratinocytes that survived senescence were serially cultivated at a density of 3.times.10.sup.5 cells per 100-mm dish. Typically the cultures reached a cell density of approximately 8.times.10.sup.6 cells within 7 days. This stable rate of cell growth was maintained through at least 59 passages, demonstrating that the cells had achieved immortality. The keratinocytes that emerged from the original senescencing population were originally designated BC-1-Ep/Spontaneous Line and are now termed NIKS. The NIKS cell line has been screened for the presence of proviral DNA sequences for HIV-1, HIV-2, EBV, CMV, HTLV-1, HTLV-2, **HBV,** HCV, B-19 parvovirus, HPV-16 and HPV-31 using either PCR or Southern analysis. None of these viruses were detected.

Detail Description Paragraph - DETX (93):

[0106] In some embodiments, the second messenger assays measure fluorescent signals from reporter molecules that respond to intracellular changes (e.g., Ca.sup.2+ concentration, membrane potential, pH, IP3, cAMP, arachidonic acid release) due to stimulation of membrane receptors and ion channels (e.g., ligand gated ion channels) (Denyer et al., Drug Discov. Today 3:323-32 (1998); Gonzales et al., Drug. Discov. Today 4:431-39 (1999)). Examples of reporter molecules include, but are not limited to, florescence resonance energy transfer systems (e.g., Cuo-lipids and oxonols, EDAN/DABCYL), calcium sensitive indicators (e.g., Fluo-3, FURA 2, INDO 1, and FLUO3/AM, **BAPTA** AM), chloride-sensitive indicators (e.g., SPQ, SPA), potassium-sensitive indicators (e.g., PBFI), sodium-sensitive indicators (e.g., SBFI), and pH sensitive indicators (e.g., BCECF).

PGPUB-DOCUMENT-NUMBER: 20020164793

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020164793 A1

TITLE: Skin substitutes and uses thereof

PUBLICATION-DATE: November 7, 2002

INVENTOR-INFORMATION:

NAME	CITY	STATE	COUNTRY	RULE-47
Conrad, Paul Barth	Madison	WI	US	
Ivarie, Cathy Ann-Rasmussen	Marshall	WI	US	
Allen-Hoffmann, Lynn	Madison	WI	US	

APPL-NO: 10/ 087641

DATE FILED: March 1, 2002

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60287898 20010501 US

non-provisional-of-provisional 60273034 20010302 US

US-CL-CURRENT: 435/371, 424/93.7

ABSTRACT:

The present invention relates to in vitro cultured skin substitutes, and in particular to improved methods for organotypic culture of skin substitutes. In some embodiments, the dermal equivalent of the skin substitute is lifted to air interface of the culture prior to seeding with keratinocytes. In other embodiments, increased concentrations of collagen are used to form the dermal equivalent. In still other embodiments, optimized media are utilized to maintain the skin equivalents.

[0001] This application claims priority to U.S. provisional patent applications serial Nos. 60/287,898, filed May 5, 2001 and 60/273,034, filed Mar. 2, 2001.

---------- KWIC ---------

Detail Description Paragraph - DETX (67):

[0091] The NIKS cells arose from the BC-1-Ep strain of human neonatal foreskin keratinocytes isolated from an apparently normal male infant. In early passages, the BC-1-Ep cells exhibited no morphological or growth characteristics that were atypical for cultured normal human keratinocytes.

Cultivated BC-1-Ep cells exhibited stratification as well as features of programmed cell death. To determine replicative lifespan, the BC-1-Ep cells were serially cultivated to senescence in standard keratinocyte growth medium at a density of 3.times.10.sup.5 cells per 100-mm dish and passaged at weekly intervals (approximately a 1:25 split). By passage 15, most keratinocytes in the population appeared senescent as judged by the presence of numerous abortive colonies which exhibited large, flat cells. However, at passage 16, keratinocytes exhibiting a small cell size were evident. By passage 17, only the small-sized keratinocytes were present in the culture and no large, senescent keratinocytes were evident. The resulting population of small keratinocytes that survived this putative crisis period appeared morphologically uniform and produced colonies of keratinocytes exhibiting typical keratinocyte characteristics including cell-cell adhesion and apparent squame production. The keratinocytes that survived senescence were serially cultivated at a density of 3.times.10.sup.5 cells per 100-mm dish. Typically the cultures reached a cell density of approximately 8.times.10.sup.6 cells within 7 days. This stable rate of cell growth was maintained through at least 59 passages, demonstrating that the cells had achieved immortality. The keratinocytes that emerged from the original senescencing population were originally designated BC-1-Ep/Spontaneous Line and are now termed NIKS. The NIKS cell line has been screened for the presence of proviral DNA sequences for HIV-1, HIV-2, EBV, CMV, HTLV-1, HTLV-2, **HBV**, HCV, B-19 parvovirus, HPV-16 and HPV-31 using either PCR or Southern analysis. None of these viruses were detected.

Detail Description Paragraph - DETX (114):

[0138] In some embodiments, the second messenger assays measure fluorescent signals from reporter molecules that respond to intracellular changes (e.g., Ca.sup.2+ concentration, membrane potential, pH, IP3, cAMP, arachidonic acid release) due to stimulation of membrane receptors and ion channels (e.g., ligand gated ion channels) (Denyer et al., Drug Discov. Today 3:323-32 (1998); Gonzales et al., Drug. Discov. Today 4:431-39 (1999)). Examples of reporter molecules include, but are not limited to, florescence resonance energy transfer systems (e.g., Cuo-lipids and oxonols, EDAN/DABCYL), calcium sensitive indicators (e.g., Fluo-3, FURA 2, INDO 1, and FLUO3/AM, **BAPTA** AM), chloride-sensitive indicators (e.g., SPQ, SPA), potassium-sensitive indicators (e.g., PBFI), sodium-sensitive indicators (e.g., SBFI), and pH sensitive indicators (e.g., BCECF).

PGPUB-DOCUMENT-NUMBER: 20020045191

PGPUB-FILING-TYPE: new

DOCUMENT-IDENTIFIER: US 20020045191 A1

TITLE: Inhibition of the SRC kinase family pathway as a method of treating **HBV** infection and hepatocellular carcinoma

PUBLICATION-DATE: April 18, 2002

US-CL-CURRENT: 435/7.1, 435/15 , 514/262.1 , 514/44 , 514/520 , 514/7 , 536/24.5

APPL-NO: 09/ 955006

DATE FILED: September 17, 2001

RELATED-US-APPL-DATA:

non-provisional-of-provisional 60232892 20000915 US

```
  * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 12:26:18 ON 08 JUL 2003

=> fil .bec,canc
COST IN U.S. DOLLARS                                  SINCE FILE      TOTAL
                                                         ENTRY    SESSION
FULL ESTIMATED COST                                       0.21       0.21

FILES 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS, NTIS,
       ESBIOBASE, BIOTECHNO, WPIDS, CANCERLIT' ENTERED AT 12:26:43 ON 08 JUL 2003
ALL COPYRIGHTS AND RESTRICTIONS APPLY.  SEE HELP USAGETERMS FOR DETAILS.

12 FILES IN THE FILE LIST

=> s hbx
FILE 'MEDLINE'
L1          310 HBX

FILE 'SCISEARCH'
L2          372 HBX

FILE 'LIFESCI'
L3          193 HBX

FILE 'BIOTECHDS'
L4           10 HBX

FILE 'BIOSIS'
L5          335 HBX

FILE 'EMBASE'
L6          263 HBX

FILE 'HCAPLUS'
L7          631 HBX

FILE 'NTIS'
L8           26 HBX

FILE 'ESBIOBASE'
L9          187 HBX

FILE 'BIOTECHNO'
L10         208 HBX

FILE 'WPIDS'
L11          12 HBX

FILE 'CANCERLIT'
L12         188 HBX

TOTAL FOR ALL FILES
L13        2735 HBX

=> s (hepatitis b virus or hbv)(8a)(inhibit? or treat?)
FILE 'MEDLINE'
        114472 HEPATITIS
        541713 B
        351997 VIRUS
         18520 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
         11224 HBV
       1037580 INHIBIT?
```

```
       1885207 TREAT?
L14       1614 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'SCISEARCH'
         82452 HEPATITIS
       1017714 B
        301493 VIRUS
         14176 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
          9354 HBV
        826673 INHIBIT?
       1387158 TREAT?
L15       1592 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'LIFESCI'
         20784 "HEPATITIS"
        183440 "B"
        175163 "VIRUS"
          8405 HEPATITIS B VIRUS
                 ("HEPATITIS"(W)"B"(W)"VIRUS")
          4363 HBV
        287526 INHIBIT?
        285470 TREAT?
L16        677 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'BIOTECHDS'
          3962 HEPATITIS
         41375 B
         39878 VIRUS
          1876 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
           501 HBV
         41448 INHIBIT?
         66864 TREAT?
L17        135 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'BIOSIS'
         98112 HEPATITIS
        637399 B
        470549 VIRUS
         24464 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
         11588 HBV
       1124809 INHIBIT?
       1630392 TREAT?
L18       1846 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'EMBASE'
         87026 "HEPATITIS"
        581745 "B"
        382372 "VIRUS"
         18894 HEPATITIS B VIRUS
                 ("HEPATITIS"(W)"B"(W)"VIRUS")
          9566 HBV
        927235 INHIBIT?
       1780510 TREAT?
L19       1680 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'HCAPLUS'
         38684 HEPATITIS
       1362645 B
        284236 VIRUS
          9915 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
```

```
          5765 HBV
       1582986 INHIBIT?
       2904887 TREAT?
L20       1583 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'NTIS'
          1201 HEPATITIS
         65826 B
          7315 VIRUS
           123 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
            82 HBV
         19865 INHIBIT?
        119153 TREAT?
L21          6 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'ESBIOBASE'
         18528 HEPATITIS
        248813 B
         82179 VIRUS
          4060 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
          3290 HBV
        333549 INHIBIT?
        418462 TREAT?
L22        615 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'BIOTECHNO'
         25714 HEPATITIS
        213079 B
        169733 VIRUS
          7893 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
          4778 HBV
        281886 INHIBIT?
        261946 TREAT?
L23        866 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'WPIDS'
          9661 HEPATITIS
       1050002 B
         31228 VIRUS
          1249 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
           687 HBV
        196535 INHIBIT?
        832275 TREAT?
L24        367 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

FILE 'CANCERLIT'
         21807 HEPATITIS
        140342 B
        121638 VIRUS
          5321 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
          3543 HBV
        240873 INHIBIT?
        518305 TREAT?
L25        827 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

TOTAL FOR ALL FILES
L26      11808 (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)

=> s l13 and l26
```

```
FILE 'MEDLINE'
L27          30 L1 AND L14

FILE 'SCISEARCH'
L28          28 L2 AND L15

FILE 'LIFESCI'
L29          20 L3 AND L16

FILE 'BIOTECHDS'
L30           2 L4 AND L17

FILE 'BIOSIS'
L31          30 L5 AND L18

FILE 'EMBASE'
L32          24 L6 AND L19

FILE 'HCAPLUS'
L33          73 L7 AND L20

FILE 'NTIS'
L34           0 L8 AND L21

FILE 'ESBIOBASE'
L35          23 L9 AND L22

FILE 'BIOTECHNO'
L36          20 L10 AND L23

FILE 'WPIDS'
L37           2 L11 AND L24

FILE 'CANCERLIT'
L38          19 L12 AND L25

TOTAL FOR ALL FILES
L39         271 L13 AND L26

=> s l13(10a)inhibit?
FILE 'MEDLINE'
       1037580 INHIBIT?
L40          50 L1 (10A)INHIBIT?

FILE 'SCISEARCH'
        826673 INHIBIT?
L41          48 L2 (10A)INHIBIT?

FILE 'LIFESCI'
        287526 INHIBIT?
L42          41 L3 (10A)INHIBIT?

FILE 'BIOTECHDS'
         41448 INHIBIT?
L43           2 L4 (10A)INHIBIT?

FILE 'BIOSIS'
       1124809 INHIBIT?
L44          48 L5 (10A)INHIBIT?

FILE 'EMBASE'
        927235 INHIBIT?
L45          46 L6 (10A)INHIBIT?
```

```
FILE 'HCAPLUS'
       1582986 INHIBIT?
L46          64 L7 (10A)INHIBIT?

FILE 'NTIS'
          19865 INHIBIT?
L47           0 L8 (10A)INHIBIT?

FILE 'ESBIOBASE'
         333549 INHIBIT?
L48          41 L9 (10A)INHIBIT?

FILE 'BIOTECHNO'
         281886 INHIBIT?
L49          40 L10(10A)INHIBIT?

FILE 'WPIDS'
         196535 INHIBIT?
L50           2 L11(10A)INHIBIT?

FILE 'CANCERLIT'
         240873 INHIBIT?
L51          46 L12(10A)INHIBIT?

TOTAL FOR ALL FILES
L52         428 L13(10A) INHIBIT?

=> s src
FILE 'MEDLINE'
L53       12549 SRC

FILE 'SCISEARCH'
L54       12063 SRC

FILE 'LIFESCI'
L55        4989 SRC

FILE 'BIOTECHDS'
L56         194 SRC

FILE 'BIOSIS'
L57       12482 SRC

FILE 'EMBASE'
L58        9235 SRC

FILE 'HCAPLUS'
L59       12601 SRC

FILE 'NTIS'
L60        1983 SRC

FILE 'ESBIOBASE'
L61        6042 SRC

FILE 'BIOTECHNO'
L62        6466 SRC

FILE 'WPIDS'
L63         633 SRC

FILE 'CANCERLIT'
L64        8510 SRC
```

```
TOTAL FOR ALL FILES
L65       87747 SRC

=> s activat?
FILE 'MEDLINE'
L66      614837 ACTIVAT?

FILE 'SCISEARCH'
L67      665949 ACTIVAT?

FILE 'LIFESCI'
L68      196755 ACTIVAT?

FILE 'BIOTECHDS'
L69       20686 ACTIVAT?

FILE 'BIOSIS'
L70      634378 ACTIVAT?

FILE 'EMBASE'
L71      536785 ACTIVAT?

FILE 'HCAPLUS'
L72     1058092 ACTIVAT?

FILE 'NTIS'
L73       27524 ACTIVAT?

FILE 'ESBIOBASE'
L74      237312 ACTIVAT?

FILE 'BIOTECHNO'
L75      216616 ACTIVAT?

FILE 'WPIDS'
L76      220259 ACTIVAT?

FILE 'CANCERLIT'
L77      165622 ACTIVAT?

TOTAL FOR ALL FILES
L78     4594815 ACTIVAT?

=> s upstream
FILE 'MEDLINE'
L79       35480 UPSTREAM

FILE 'SCISEARCH'
L80       40216 UPSTREAM

FILE 'LIFESCI'
L81       24318 UPSTREAM

FILE 'BIOTECHDS'
L82        3817 UPSTREAM

FILE 'BIOSIS'
L83       40464 UPSTREAM

FILE 'EMBASE'
L84       31014 UPSTREAM

FILE 'HCAPLUS'
L85       54395 UPSTREAM
```

```
FILE 'NTIS'
L86        6087 UPSTREAM

FILE 'ESBIOBASE'
L87       20721 UPSTREAM

FILE 'BIOTECHNO'
L88       26698 UPSTREAM

FILE 'WPIDS'
L89       56117 UPSTREAM

FILE 'CANCERLIT'
L90       10465 UPSTREAM

TOTAL FOR ALL FILES
L91      349792 UPSTREAM

=> s l65 and l78(5a)l91
FILE 'MEDLINE'
          2462 L66(5A)L79
L92         86 L53 AND L66(5A)L79

FILE 'SCISEARCH'
          2554 L67(5A)L80
L93         88 L54 AND L67(5A)L80

FILE 'LIFESCI'
          1577 L68(5A)L81
L94         34 L55 AND L68(5A)L81

FILE 'BIOTECHDS'
           151 L69(5A)L82
L95          0 L56 AND L69(5A)L82

FILE 'BIOSIS'
          2676 L70(5A)L83
L96         93 L57 AND L70(5A)L83

FILE 'EMBASE'
          2172 L71(5A)L84
L97         69 L58 AND L71(5A)L84

FILE 'HCAPLUS'
          3184 L72(5A)L85
L98         80 L59 AND L72(5A)L85

FILE 'NTIS'
            13 L73(5A)L86
L99          0 L60 AND L73(5A)L86

FILE 'ESBIOBASE'
          1615 L74(5A)L87
L100        61 L61 AND L74(5A)L87

FILE 'BIOTECHNO'
          1717 L75(5A)L88
L101        46 L62 AND L75(5A)L88

FILE 'WPIDS'
           223 L76(5A)L89
L102         0 L63 AND L76(5A)L89
```

```
FILE 'CANCERLIT'
           978 L77(5A)L90
L103        52 L64 AND L77(5A)L90

TOTAL FOR ALL FILES
L104       609 L65 AND L78(5A) L91

=> s l65 and (hbv or hbx)
FILE 'MEDLINE'
         11224 HBV
           310 HBX
L105        14 L53 AND (HBV OR HBX)

FILE 'SCISEARCH'
          9354 HBV
           372 HBX
L106        11 L54 AND (HBV OR HBX)

FILE 'LIFESCI'
          4363 HBV
           193 HBX
L107         7 L55 AND (HBV OR HBX)

FILE 'BIOTECHDS'
           501 HBV
            10 HBX
L108         1 L56 AND (HBV OR HBX)

FILE 'BIOSIS'
         11588 HBV
           335 HBX
L109        13 L57 AND (HBV OR HBX)

FILE 'EMBASE'
          9566 HBV
           263 HBX
L110         8 L58 AND (HBV OR HBX)

FILE 'HCAPLUS'
          5765 HBV
           631 HBX
L111        15 L59 AND (HBV OR HBX)

FILE 'NTIS'
            82 HBV
            26 HBX
L112         0 L60 AND (HBV OR HBX)

FILE 'ESBIOBASE'
          3290 HBV
           187 HBX
L113         7 L61 AND (HBV OR HBX)

FILE 'BIOTECHNO'
          4778 HBV
           208 HBX
L114         7 L62 AND (HBV OR HBX)

FILE 'WPIDS'
           687 HBV
            12 HBX
L115         4 L63 AND (HBV OR HBX)

FILE 'CANCERLIT'
```

```
          3543 HBV
           188 HBX
L116         8 L64 AND (HBV OR HBX)

TOTAL FOR ALL FILES
L117        95 L65 AND (HBV OR HBX)

=> s (139 or 152 or 1104 or 1117) and py=<1998 range=2002,
FILE 'MEDLINE'
'2002,' IS NOT A VALID RANGE FOR FILE 'MEDLINE'
SEARCH ENDED BY USER

FILE 'SCISEARCH'
            49 PY=<1998
L118         0 (L28 OR L41 OR L93 OR L106) AND PY=<1998

FILE 'LIFESCI'
           793 PY=<1998
L119         0 (L29 OR L42 OR L94 OR L107) AND PY=<1998

FILE 'BIOTECHDS'
            71 PY=<1998
                 (PY=<1998)
L120         0 (L30 OR L43 OR L95 OR L108) AND PY=<1998

FILE 'BIOSIS'
         70438 PY=<1998
L121         0 (L31 OR L44 OR L96 OR L109) AND PY=<1998

FILE 'EMBASE'
           131 PY=<1998
L122         0 (L32 OR L45 OR L97 OR L110) AND PY=<1998

FILE 'HCAPLUS'
          2383 PY=<1998
L123         0 (L33 OR L46 OR L98 OR L111) AND PY=<1998

FILE 'NTIS'
          3544 PY=<1998
L124         0 (L34 OR L47 OR L99 OR L112) AND PY=<1998

FILE 'ESBIOBASE'
           160 PY=<1998
L125         0 (L35 OR L48 OR L100 OR L113) AND PY=<1998

FILE 'BIOTECHNO'
       1165533 PY=<1998
L126        46 (L36 OR L49 OR L101 OR L114) AND PY=<1998

FILE 'WPIDS'
          9094 PY=<1998
                 (PY=<1998)
L127         0 (L37 OR L50 OR L102 OR L115) AND PY=<1998

FILE 'CANCERLIT'
         36109 PY=<1998
L128         4 (L38 OR L51 OR L103 OR L116) AND PY=<1998

TOTAL FOR ALL FILES
L129        50 (L39 OR L52 OR L104 OR L117) AND PY=<1998

=> dup rem l129
PROCESSING COMPLETED FOR L129
L130        46 DUP REM L129 (4 DUPLICATES REMOVED)
```

=> d tot

L130 ANSWER 1 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI The **hepatitis B virus HBx** protein **inhibits** caspase 3 activity
SO Journal of Biological Chemistry, **(11 DEC 1998)**, 273/50 (33347-33353), 32 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
AU Gottlob K.; Fulco M.; Levrero M.; Graessmann A.
AN 1998:29005712 BIOTECHNO

L130 ANSWER 2 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Hepatitis B x protein inhibits p53-dependent DNA repair in primary mouse hepatocytes
SO Journal of Biological Chemistry, **(11 DEC 1998)**, 273/50 (33327-33332), 53 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
AU Prost S.; Ford J.M.; Taylor C.; Doig J.; Harrison D.J.
AN 1998:29005709 BIOTECHNO

L130 ANSWER 3 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Differential activation of p70 and p85 S6 kinase isoforms during cardiac hypertrophy in the adult mammal
SO Journal of Biological Chemistry, **(18 SEP 1998)**, 273/38 (24610-24619), 57 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
AU Laser M.; Kasi V.S.; Hamawaki M.; Cooper IV G.; Kerr C.M.; Kuppuswamy D.
AN 1998:28454957 BIOTECHNO

L130 ANSWER 4 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI A novel regulator of p21-activated kinases
SO Journal of Biological Chemistry, **(11 SEP 1998)**, 273/37 (23633-23636), 32 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
AU Bagrodia S.; Taylor S.J.; Jordon K.A.; Van Aelst L.; Cerione R.A.
AN 1998:28435688 BIOTECHNO

L130 ANSWER 5 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Liver-specific enhancer II is the target for the p53-mediated inhibition of hepatitis B viral gene expression
SO Journal of Biological Chemistry, **(31 JUL 1998)**, 273/31 (19786-19791), 43 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
AU Lee H.; Hong Tae Kim; Yun Y.
AN 1998:28367039 BIOTECHNO

L130 ANSWER 6 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI The **src** homology 2-containing inositol phosphatase (SHIP) is the gatekeeper of mast cell degranulation
SO Proceedings of the National Academy of Sciences of the United States of America, **(15 SEP 1998)**, 95/19 (11330-11335), 32 reference(s)
CODEN: PNASA6 ISSN: 0027-8424
AU Huber M.; Helgason C.D.; Damen J.E.; Liu L.; Humphries R.K.; Krystal G.
AN 1998:28450128 BIOTECHNO

L130 ANSWER 7 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI RMP, a novel RNA polymerase II subunit 5-interacting protein, counteracts transactivation by hepatitis B virus x protein
SO Molecular and Cellular Biology, **(1998)**, 18/12 (7546-7555), 55 reference(s)
CODEN: MCEBD4 ISSN: 0270-7306
AU Dorjsuren D.; Lin Y.; Wei W.; Yamashita T.; Nomura T.; Hayashi N.; Murakami S.

AN 1998:28533073 BIOTECHNO

L130 ANSWER 8 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Targeted disruption of SHIP leads to Steel factor-induced degranulation of mast cells
SO EMBO Journal, **(15 DEC 1998)**, 17/24 (7311-7319), 33 reference(s)
CODEN: EMJODG ISSN: 0261-4189
AU Huber M.; Helgason C.D.; Scheid M.P.; Duronio V.; Humphries R.K.; Krystal G.
AN 1998:29002700 BIOTECHNO

L130 ANSWER 9 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Repression of Stat3 activity by activation of mitogen-activated protein kinase (MAPK)
SO Oncogene, **(17 DEC 1998)**, 17/24 (3157-3167), 45 reference(s)
CODEN: ONCNES ISSN: 0950-9232
AU Jain N.; Zhang T.; Fong S.L.; Lim C.P.; Cao X.
AN 1998:29020811 BIOTECHNO

L130 ANSWER 10 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Cloning and characterization of a novel **hepatitis B virus** x binding protein that **inhibits** viral replication
SO Journal of Virology, **(1998)**, 72/3 (1737-1743), 34 reference(s)
CODEN: JOVIAM ISSN: 0022-538X
AU Melegari M.; Scaglioni P.P.; Wands J.R.
AN 1998:28100722 BIOTECHNO

L130 ANSWER 11 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI X-gene product of hepatitis B virus induces apoptosis in liver cells
SO Journal of Biological Chemistry, **(1998)**, 273/1 (381-385), 45 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
AU Kim H.; Lee H.; Yun Y.
AN 1998:28042221 BIOTECHNO

L130 ANSWER 12 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Hepatitis B virus X protein interferes with cellular DNA repair
SO Journal of Virology, **(1998)**, 72/1 (266-272), 60 reference(s)
CODEN: JOVIAM ISSN: 0022-538X
AU Becker S.A.; Lee T.-H.; Butel J.S.; Slagle B.L.
AN 1998:28048836 BIOTECHNO

L130 ANSWER 13 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Heat shock activates c-**Src** tyrosine kinases and phosphatidylinositol 3- kinase in NIH3T3 fibroblasts
SO Journal of Biological Chemistry, **(1997)**, 272/49 (31196-31202), 31 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
AU Lin R.Z.; Hu Z.-W.; Chin J.H.; Hoffman B.B.
AN 1997:27527571 BIOTECHNO

L130 ANSWER 14 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Syk and Fyn are required by mouse megakaryocytes for the rise in intracellular calcium induced by a collagen-related peptide
SO Journal of Biological Chemistry, **(1997)**, 272/44 (27539-27542), 44 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
AU Melford S.K.; Turner M.; Briddon S.J.; Tybulewicz V.L.J.; Watson S.P.
AN 1997:27473543 BIOTECHNO

L130 ANSWER 15 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Activating transcription factor 2 (ATF2) down-regulates hepatitis B virus X promoter activity by the competition for the activating protein 1 binding site and the formation of the ATF2-Jun heterodimer

SO Journal of Biological Chemistry, (**1997**), 272/27 (16934-16939), 50 reference(s)
CODEN: JBCHA3 ISSN: 0021-9258
AU Cheol Yong Choi; Byung Hyune Choi; Geon Tae Park; Hyune Mo Rho
AN 1997:27289795 BIOTECHNO

L130 ANSWER 16 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Hepatitis B virus X protein and p53 tumor suppressor interactions in the modulation of apoptosis
SO Proceedings of the National Academy of Sciences of the United States of America, (**1997**), 94/26 (14707-14712), 58 reference(s)
CODEN: PNASA6 ISSN: 0027-8424
AU Elmore L.W.; Hancock A.R.; Chang S.-F.; Wang X.W.; Chang S.; Callahan C.P.; Geller D.A.; Will H.; Harris C.C.
AN 1997:28041438 BIOTECHNO

L130 ANSWER 17 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Hepatitis B virus HBx protein sensitizes cells to apoptotic killing by tumor necrosis factor .alpha.
SO Proceedings of the National Academy of Sciences of the United States of America, (**1997**), 94/16 (8744-8749), 42 reference(s)
CODEN: PNASA6 ISSN: 0027-8424
AU Su F.; Schneider R.J.
AN 1997:27335110 BIOTECHNO

L130 ANSWER 18 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Activation of **Src** family kinases by hepatitis B virus **HBx** protein and coupled signaling to Ras
SO Molecular and Cellular Biology, (**1997**), 17/11 (6427-6436), 75 reference(s)
CODEN: MCEBD4 ISSN: 0270-7306
AU Klein N.P.; Schneider R.J.
AN 1997:27451188 BIOTECHNO

L130 ANSWER 19 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI The transactivation and p53-interacting functions of hepatitis B virus X protein are mutually interfering but distinct
SO Cancer Research, (**1997**), 57/22 (5137-5142), 51 reference(s)
CODEN: CNREA8 ISSN: 0008-5472
AU Lin Y.; Nomura T.; Yamashita T.; Dorjsuren D.; Tang H.; Murakami S.
AN 1997:27498132 BIOTECHNO

L130 ANSWER 20 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Increased enzymatic activity of the T-cell antigen receptor-associated Fyn protein tyrosine kinase in asymptomatic patients infected with the human immunodeficiency virus
SO Blood, (**1997**), 90/9 (3603-3612), 47 reference(s)
CODEN: BLOOAW ISSN: 0006-4971
AU Phipps D.J.; Yousefi S.; Branch D.R.
AN 1997:27473430 BIOTECHNO

L130 ANSWER 21 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI MEK1 mediates a positive feedback on Raf-1 activity independently of Ras and **Src**
SO Oncogene, (**1997**), 15/13 (1503-1511), 50 reference(s)
CODEN: ONCNES ISSN: 0950-9232
AU Zimmermannn S.; Rommel C.; Ziogas A.; Lovric J.; Moelling K.; Radziwill G.
AN 1997:27464643 BIOTECHNO

L130 ANSWER 22 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI **Inhibition** of hepatocellular carcinoma development in **hepatitis B virus** transfected mice by low dietary casein

SO Hepatology, (**1997**), 26/5 (1351-4354), 32 reference(s)
CODEN: HPTLD0 ISSN: 0270-9139
AU Cheng Z.; Hu J.; King J.; Jay G.; Campbell T.C.
AN 1997:27509324 BIOTECHNO

L130 ANSWER 23 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Anti-ganglioside monoclonal antibody AA4 selectively inhibits IgE-induced signal transduction pathways in rat basophilic leukemia cells
SO Molecular Immunology, (**1997**), 34/3 (227-235), 27 reference(s)
CODEN: IMCHAZ ISSN: 0161-5890
AU Stephan V.; Seibt A.; Dukanovic D.; Skasa M.; Swaim W.D.; Berenstein E.H.; Siraganian R.P.; Wahn V.
AN 1997:27295271 BIOTECHNO

L130 ANSWER 24 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Mutant of insulin receptor substrate-1 incapable of activating phosphatidylinositol 3-kinase did not mediate insulin-stimulated maturation of Xenopus laevis oocytes
SO Journal of Biological Chemistry, (**1996**), 271/45 (28677-28681)
CODEN: JBCHA3 ISSN: 0021-9258
AU Yamamoto-Honda R.; Honda Z.; Ueki K.; Tobe K.; Kaburagi Y.; Takahashi Y.; Tamemoto H.; Suzuki T.; Itoh K.; Akanuma Y.; Yazaki Y.; Kadowaki T.
AN 1996:26374696 BIOTECHNO

L130 ANSWER 25 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Negative signaling via Fc.gamma.RIIB1 in B cells blocks phospholipase C.gamma.2 tyrosine phosphorylation but not Syk or Lyn activation
SO Journal of Biological Chemistry, (**1996**), 271/33 (20182-20186)
CODEN: JBCHA3 ISSN: 0021-9258
AU Sarkar S.; Schlottmann K.; Cooney D.; Coggeshall K.M.
AN 1996:26281775 BIOTECHNO

L130 ANSWER 26 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Activation of the mitogen-activated protein kinase pathway by fMet-Leu-Phe in the absence of Lyn and tyrosine phosphorylation of SHC in transfected cells
SO Journal of Biological Chemistry, (**1996**), 271/22 (13244-13249)
CODEN: JBCHA3 ISSN: 0021-9258
AU Torres M.; Ye R.D.
AN 1996:26175908 BIOTECHNO

L130 ANSWER 27 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Mechanical strain induces pp60(**src**) activation and translocation to cytoskeleton in fetal rat lung cells
SO Journal of Biological Chemistry, (**1996**), 271/12 (7066-7071)
CODEN: JBCHA3 ISSN: 0021-9258
AU Liu M.; Qin Y.; Liu J.; Tanswell A.K.; Post M.
AN 1996:26104142 BIOTECHNO

L130 ANSWER 28 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Hepatitis B virus HBx protein activates transcription factor NF-.kappa.B by acting on multiple cytoplasmic inhibitors of rel-related proteins
SO Journal of Virology, (**1996**), 70/7 (4558-4566)
CODEN: JOVIAM ISSN: 0022-538X
AU Su F.; Schneider R.J.
AN 1996:26191145 BIOTECHNO

L130 ANSWER 29 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Signaling by ectopically expressed Drosophila Src64 requires the protein-tyrosine phosphatase corkscrew and the adapter downstream of receptor kinases
SO Cell Growth and Differentiation, (**1996**), 7/11 (1435-1441)
CODEN: CGDIE7 ISSN: 1044-9523
AU Cooper J.A.; Simon M.A.; Kussick S.J.

AN 1996:26378337 BIOTECHNO

L130 ANSWER 30 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI The effect of **hepatitis B virus** X gene expression on response to growth **inhibition** by transforming growth factor-.beta.1
SO Biochemical and Biophysical Research Communications, (**1996**), 222/3 (770-773)
CODEN: BBRCA0 ISSN: 0006-291X
AU Oshikawa O.; Tamura S.; Kawata S.; Ito N.; Tsushima H.; Kiso S.; Matsuda Y.; Yamada A.; Tamai S.; Matsuzawa Y.
AN 1996:26194827 BIOTECHNO

L130 ANSWER 31 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Hypoxia and hypoxia/reoxygenation activate **Src** family tyrosine kinases and p21(ras) in cultured rat cardiac myocytes
SO Biochemical and Biophysical Research Communications, (**1996**), 226/2 (530-535)
CODEN: BBRCA0 ISSN: 0006-291X
AU Seko Y.; Tobe K.; Takahashi N.; Kaburagi Y.; Kadowaki T.; Yazaki Y.
AN 1996:26331935 BIOTECHNO

L130 ANSWER 32 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI In vivo **inhibition** of **hepatitis B virus** gene expression by antisense phosphorothioate oligonucleotides
SO Biochemical and Biophysical Research Communications, (**1996**), 218/1 (217-223)
CODEN: BBRCA0 ISSN: 0006-291X
AU Moriya K.; Matsukura M.; Kurokawa K.; Koike K.
AN 1996:26034514 BIOTECHNO

L130 ANSWER 33 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI HIV envelope-directed signaling aberrancies and cell death of CD4.sup.+ T cells in the absence of TCR co-stimulation
SO International Immunology, (**1996**), 8/1 (65-74)
CODEN: INIMEN ISSN: 0953-8178
AU Tian H.; Lempicki R.; King L.; Donoghue E.; Samelson L.E.; Cohen D.I.
AN 1996:26029269 BIOTECHNO

L130 ANSWER 34 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Isolation and characterization of a novel dual specific phosphatase, HVH2, which selectively dephosphorylates the mitogen-activated protein kinase
SO Journal of Biological Chemistry, (**1995**), 270/13 (7197-7203)
CODEN: JBCHA3 ISSN: 0021-9258
AU Guan K.-L.; Butch E.
AN 1995:25106764 BIOTECHNO

L130 ANSWER 35 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.DUPLICATE
TI Abrogation of p53-induced apoptosis by the hepatitis B virus X gene
SO Cancer Research, (**1995**), 55/24 (6012-6016)
CODEN: CNREA8 ISSN: 0008-5472
AU Xin Wei Wang; Gibson M.K.; Vermeulen W.; Yeh H.; Forrester K.; Sturzbecher - H.W.; Hoeijmakers J.H.J.; Harris C.C.
AN 1995:25366975 BIOTECHNO

L130 ANSWER 36 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.DUPLICATE
TI Direct interaction of the **hepatitis B virus** **HBx** protein with p53 leads to **inhibition** by **HBx** of p53 response element-directed transactivation
SO Journal of Virology, (**1995**), 69/3 (1851-1859)
CODEN: JOVIAM ISSN: 0022-538X
AU Truant R.; Antunovic J.; Greenblatt J.; Prives C.; Cromlish J.A.

AN 1995:25056198 BIOTECHNO

L130 ANSWER 37 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Mechanisms regulating Raf-1 activity in signal transduction pathways
SO Molecular Reproduction and Development, (**1995**), 42/4 (507-514)
CODEN: MREDEE ISSN: 1040-452X
AU Morrison D.K.
AN 1995:25367307 BIOTECHNO

L130 ANSWER 38 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Hepatitis B virus HBx protein activates Ras-GTP complex formation and establishes a Ras, Raf, MAP kinase signaling cascade
SO Proceedings of the National Academy of Sciences of the United States of America, (**1994**), 91/22 (10350-10354)
CODEN: PNASA6 ISSN: 0027-8424
AU Benn J.; Schneider R.J.
AN 1994:24328994 BIOTECHNO

L130 ANSWER 39 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Mitogen-activated protein kinase/extracellular signal-regulated protein kinase activation by oncogenes, serum, and 12-O-tetradecanoylphorbol-13-acetate requires Raf and is necessary for transformation
SO Journal of Biological Chemistry, (**1994**), 269/9 (7030-7035)
CODEN: JBCHA3 ISSN: 0021-9258
AU Troppmair J.; Bruder J.T.; Munoz H.; Lloyd P.A.; Kyriakis J.; Banerjee P.; Avruch J.; Rapp U.R.
AN 1994:24191104 BIOTECHNO

L130 ANSWER 40 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Role of SH-PTP2, a protein-tyrosine phosphatase with **Src** homology 2 domains, in insulin-stimulated Ras activation
SO Molecular and Cellular Biology, (**1994**), 14/10 (6674-6682)
CODEN: MCEBD4 ISSN: 0270-7306
AU Noguchi T.; Matozaki T.; Horita K.; Fujioka Y.; Kasuga M.
AN 1994:24299736 BIOTECHNO

L130 ANSWER 41 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.DUPLICATE
TI p56(lck)-Independent activation and tyrosine phosphorylation of p72(syk) by T-cell antigen receptor/CD3 stimulation
SO Proceedings of the National Academy of Sciences of the United States of America, (**1994**), 91/12 (5301-5305)
CODEN: PNASA6 ISSN: 0027-8424
AU Couture C.; Baier G.; Altman A.; Mustelin T.
AN 1994:24174314 BIOTECHNO

L130 ANSWER 42 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.DUPLICATE
TI **Hepatitis B virus** X protein **inhibits** p53 sequence-specific DNA binding, transcriptional activity, and association with transcription factor ERCC3
SO Proceedings of the National Academy of Sciences of the United States of America, (**1994**), 91/6 (2230-2234)
CODEN: PNASA6 ISSN: 0027-8424
AU Xin Wei Wang; Forrester K.; Yeh H.; Feitelson M.A.; Gu J.-R.; Harris C.C.
AN 1994:24092077 BIOTECHNO

L130 ANSWER 43 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.
TI Transactivation of human hepatitis B virus X protein, HBx, operates through a mechanism distinct from protein kinase C and okadaic acid activation pathways
SO Virology, (**1994**), 199/1 (243-246)
CODEN: VIRLAX ISSN: 0042-6822
AU Murakami S.; Cheong J.; Ohno S.; Matsushima K.; Kaneko S.
AN 1994:24170446 BIOTECHNO

```
L130  ANSWER 44 OF 46  BIOTECHNO  COPYRIGHT 2003 Elsevier Science B.V.
TI    Critical tyrosine residues regulate the enzymatic and biological activity
      of Raf-1 kinase
SO    Molecular and Cellular Biology, (1993), 13/11 (7170-7179)
      CODEN: MCEBD4  ISSN: 0270-7306
AU    Fabian J.R.; Daar I.O.; Morrison D.K.
AN    1993:23321169   BIOTECHNO

L130  ANSWER 45 OF 46  BIOTECHNO  COPYRIGHT 2003 Elsevier Science B.V.
TI    Activation of Ras by insulin in 3T3 L1 cells does not involve GTPase-
      activating protein phosphorylation
SO    Journal of Biological Chemistry, (1992), 267/29 (21124-21131)
      CODEN: JBCHA3  ISSN: 0021-9258
AU    Porras A.; Nebreda A.R.; Benito M.; Santos E.
AN    1992:22326761   BIOTECHNO

L130  ANSWER 46 OF 46  BIOTECHNO  COPYRIGHT 2003 Elsevier Science B.V.
TI    Expression of oncogenes and tumor suppressor genes in human
      hepatocellular carcinoma and hepatoblastoma cell lines
SO    Journal of Medical Virology, (1992), 38/4 (235-239)
      CODEN: JMVIDB  ISSN: 0146-6615
AU    Farshid M.; Tabor E.
AN    1992:23000548   BIOTECHNO


=> save temp src/a l130
ANSWER SET L130 HAS BEEN SAVED AS 'SRC/A'

=> fil .becpat
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                               73.51      73.72

FILES 'BIOTECHDS, HCAPLUS, WPIDS' ENTERED AT 12:35:34 ON 08 JUL 2003
ALL COPYRIGHTS AND RESTRICTIONS APPLY.  SEE HELP USAGETERMS FOR DETAILS.

3 FILES IN THE FILE LIST

=> s (l39 or l52 or l104 or l117) and wo/pc and pry=<1998 range=2000,
FILE 'BIOTECHDS'
         23724 WO/PC
          8401 PRY=<1998
                 (PRY=<1998)
L131        0 (L30 OR L43 OR L95 OR L108) AND WO/PC AND PRY=<1998

FILE 'HCAPLUS'
        154693 WO/PC
        156563 PRY=<1998
L132        0 (L33 OR L46 OR L98 OR L111) AND WO/PC AND PRY=<1998

FILE 'WPIDS'
        330171 WO/PC
        704797 PRY=<1998
                 (PRY=<1998)
L133        0 (L37 OR L50 OR L102 OR L115) AND WO/PC AND PRY=<1998

TOTAL FOR ALL FILES
L134        0 (L39 OR L52 OR L104 OR L117) AND WO/PC AND PRY=<1998

=> log y
COST IN U.S. DOLLARS                          SINCE FILE      TOTAL
                                                   ENTRY    SESSION
FULL ESTIMATED COST                                7.06      80.78
```

```
STN INTERNATIONAL LOGOFF AT 12:36:44 ON 08 JUL 2003

  * * * * * * * * * * * * * * STN  Columbus  * * * * * * * * * * * * * * *

FILE 'HOME' ENTERED AT 15:07:40 ON 08 JUL 2003

=> fil .bec,canc
COST IN U.S. DOLLARS                                    SINCE FILE      TOTAL
                                                           ENTRY    SESSION
FULL ESTIMATED COST                                         0.21       0.21

FILES 'MEDLINE, SCISEARCH, LIFESCI, BIOTECHDS, BIOSIS, EMBASE, HCAPLUS, NTIS,
       ESBIOBASE, BIOTECHNO, WPIDS, CANCERLIT' ENTERED AT 15:07:50 ON 08 JUL 2003
ALL COPYRIGHTS AND RESTRICTIONS APPLY.  SEE HELP USAGETERMS FOR DETAILS.

12 FILES IN THE FILE LIST

=> act src/a
L1  (       310)SEA FILE=MEDLINE ABB=ON  HBX
L2  (       372)SEA FILE=SCISEARCH ABB=ON  HBX
L3  (       193)SEA FILE=LIFESCI ABB=ON  HBX
L4  (        10)SEA FILE=BIOTECHDS ABB=ON  HBX
L5  (       335)SEA FILE=BIOSIS ABB=ON  HBX
L6  (       263)SEA FILE=EMBASE ABB=ON  HBX
L7  (       631)SEA FILE=HCAPLUS ABB=ON  HBX
L8  (        26)SEA FILE=NTIS ABB=ON  HBX
L9  (       187)SEA FILE=ESBIOBASE ABB=ON  HBX
L10 (       208)SEA FILE=BIOTECHNO ABB=ON  HBX
L11 (        12)SEA FILE=WPIDS ABB=ON  HBX
L12 (       188)SEA FILE=CANCERLIT ABB=ON  HBX
L13 (      2735)SEA HBX
L14 (      1614)SEA FILE=MEDLINE ABB=ON  (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT
L15 (      1592)SEA FILE=SCISEARCH ABB=ON  (HEPATITIS B VIRUS OR HBV)(8A)(INHIB
L16 (       677)SEA FILE=LIFESCI ABB=ON  (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT
L17 (       135)SEA FILE=BIOTECHDS ABB=ON  (HEPATITIS B VIRUS OR HBV)(8A)(INHIB
L18 (      1846)SEA FILE=BIOSIS ABB=ON  (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT?
L19 (      1680)SEA FILE=EMBASE ABB=ON  (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT?
L20 (      1583)SEA FILE=HCAPLUS ABB=ON  (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT
L21 (         6)SEA FILE=NTIS ABB=ON  (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? O
L22 (       615)SEA FILE=ESBIOBASE ABB=ON  (HEPATITIS B VIRUS OR HBV)(8A)(INHIB
L23 (       866)SEA FILE=BIOTECHNO ABB=ON  (HEPATITIS B VIRUS OR HBV)(8A)(INHIB
L24 (       367)SEA FILE=WPIDS ABB=ON  (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT?
L25 (       827)SEA FILE=CANCERLIT ABB=ON  (HEPATITIS B VIRUS OR HBV)(8A)(INHIB
L26 (     11808)SEA (HEPATITIS B VIRUS OR HBV)(8A)(INHIBIT? OR TREAT?)
L27 (        30)SEA FILE=MEDLINE ABB=ON  L1 AND L14
L28 (        28)SEA FILE=SCISEARCH ABB=ON  L2 AND L15
L29 (        20)SEA FILE=LIFESCI ABB=ON  L3 AND L16
L30 (         2)SEA FILE=BIOTECHDS ABB=ON  L4 AND L17
L31 (        30)SEA FILE=BIOSIS ABB=ON  L5 AND L18
L32 (        24)SEA FILE=EMBASE ABB=ON  L6 AND L19
L33 (        73)SEA FILE=HCAPLUS ABB=ON  L7 AND L20
L34 (         0)SEA FILE=NTIS ABB=ON  L8 AND L21
L35 (        23)SEA FILE=ESBIOBASE ABB=ON  L9 AND L22
L36 (        20)SEA FILE=BIOTECHNO ABB=ON  L10 AND L23
L37 (         2)SEA FILE=WPIDS ABB=ON  L11 AND L24
L38 (        19)SEA FILE=CANCERLIT ABB=ON  L12 AND L25
L39 (       271)SEA L13 AND L26
L40 (        50)SEA FILE=MEDLINE ABB=ON  L1 (10A)INHIBIT?
L41 (        48)SEA FILE=SCISEARCH ABB=ON  L2 (10A)INHIBIT?
L42 (        41)SEA FILE=LIFESCI ABB=ON  L3 (10A)INHIBIT?
L43 (         2)SEA FILE=BIOTECHDS ABB=ON  L4 (10A)INHIBIT?
L44 (        48)SEA FILE=BIOSIS ABB=ON  L5 (10A)INHIBIT?
L45 (        46)SEA FILE=EMBASE ABB=ON  L6 (10A)INHIBIT?
L46 (        64)SEA FILE=HCAPLUS ABB=ON  L7 (10A)INHIBIT?
```

```
L47 (         0)SEA FILE=NTIS ABB=ON  L8 (10A)INHIBIT?
L48 (        41)SEA FILE=ESBIOBASE ABB=ON  L9 (10A)INHIBIT?
L49 (        40)SEA FILE=BIOTECHNO ABB=ON  L10(10A)INHIBIT?
L50 (         2)SEA FILE=WPIDS ABB=ON  L11(10A)INHIBIT?
L51 (        46)SEA FILE=CANCERLIT ABB=ON  L12(10A)INHIBIT?
L52 (       428)SEA L13(10A) INHIBIT?
L53 (     12549)SEA FILE=MEDLINE ABB=ON  SRC
L54 (     12063)SEA FILE=SCISEARCH ABB=ON  SRC
L55 (      4989)SEA FILE=LIFESCI ABB=ON  SRC
L56 (       194)SEA FILE=BIOTECHDS ABB=ON  SRC
L57 (     12482)SEA FILE=BIOSIS ABB=ON  SRC
L58 (      9235)SEA FILE=EMBASE ABB=ON  SRC
L59 (     12601)SEA FILE=HCAPLUS ABB=ON  SRC
L60 (      1983)SEA FILE=NTIS ABB=ON  SRC
L61 (      6042)SEA FILE=ESBIOBASE ABB=ON  SRC
L62 (      6466)SEA FILE=BIOTECHNO ABB=ON  SRC
L63 (       633)SEA FILE=WPIDS ABB=ON  SRC
L64 (      8510)SEA FILE=CANCERLIT ABB=ON  SRC
L65 (     87747)SEA SRC
L66 (    614837)SEA FILE=MEDLINE ABB=ON  ACTIVAT?
L67 (    665949)SEA FILE=SCISEARCH ABB=ON  ACTIVAT?
L68 (    196755)SEA FILE=LIFESCI ABB=ON  ACTIVAT?
L69 (     20686)SEA FILE=BIOTECHDS ABB=ON  ACTIVAT?
L70 (    634378)SEA FILE=BIOSIS ABB=ON  ACTIVAT?
L71 (    536785)SEA FILE=EMBASE ABB=ON  ACTIVAT?
L72 (   1058092)SEA FILE=HCAPLUS ABB=ON  ACTIVAT?
L73 (     27524)SEA FILE=NTIS ABB=ON  ACTIVAT?
L74 (    237312)SEA FILE=ESBIOBASE ABB=ON  ACTIVAT?
L75 (    216616)SEA FILE=BIOTECHNO ABB=ON  ACTIVAT?
L76 (    220259)SEA FILE=WPIDS ABB=ON  ACTIVAT?
L77 (    165622)SEA FILE=CANCERLIT ABB=ON  ACTIVAT?
L78 (   4594815)SEA ACTIVAT?
L79 (     35480)SEA FILE=MEDLINE ABB=ON  UPSTREAM
L80 (     40216)SEA FILE=SCISEARCH ABB=ON  UPSTREAM
L81 (     24318)SEA FILE=LIFESCI ABB=ON  UPSTREAM
L82 (      3817)SEA FILE=BIOTECHDS ABB=ON  UPSTREAM
L83 (     40464)SEA FILE=BIOSIS ABB=ON  UPSTREAM
L84 (     31014)SEA FILE=EMBASE ABB=ON  UPSTREAM
L85 (     54395)SEA FILE=HCAPLUS ABB=ON  UPSTREAM
L86 (      6087)SEA FILE=NTIS ABB=ON  UPSTREAM
L87 (     20721)SEA FILE=ESBIOBASE ABB=ON  UPSTREAM
L88 (     26698)SEA FILE=BIOTECHNO ABB=ON  UPSTREAM
L89 (     56117)SEA FILE=WPIDS ABB=ON  UPSTREAM
L90 (     10465)SEA FILE=CANCERLIT ABB=ON  UPSTREAM
L91 (    349792)SEA UPSTREAM
L92 (        86)SEA FILE=MEDLINE ABB=ON  L53 AND L66(5A)L79
L93 (        88)SEA FILE=SCISEARCH ABB=ON  L54 AND L67(5A)L80
L94 (        34)SEA FILE=LIFESCI ABB=ON  L55 AND L68(5A)L81
L95 (         0)SEA FILE=BIOTECHDS ABB=ON  L56 AND L69(5A)L82
L96 (        93)SEA FILE=BIOSIS ABB=ON  L57 AND L70(5A)L83
L97 (        69)SEA FILE=EMBASE ABB=ON  L58 AND L71(5A)L84
L98 (        80)SEA FILE=HCAPLUS ABB=ON  L59 AND L72(5A)L85
L99 (         0)SEA FILE=NTIS ABB=ON  L60 AND L73(5A)L86
L100(        61)SEA FILE=ESBIOBASE ABB=ON  L61 AND L74(5A)L87
L101(        46)SEA FILE=BIOTECHNO ABB=ON  L62 AND L75(5A)L88
L102(         0)SEA FILE=WPIDS ABB=ON  L63 AND L76(5A)L89
L103(        52)SEA FILE=CANCERLIT ABB=ON  L64 AND L77(5A)L90
L104(       609)SEA L65 AND L78(5A) L91
L105(        14)SEA FILE=MEDLINE ABB=ON  L53 AND (HBV OR HBX)
L106(        11)SEA FILE=SCISEARCH ABB=ON  L54 AND (HBV OR HBX)
L107(         7)SEA FILE=LIFESCI ABB=ON  L55 AND (HBV OR HBX)
L108(         1)SEA FILE=BIOTECHDS ABB=ON  L56 AND (HBV OR HBX)
L109(        13)SEA FILE=BIOSIS ABB=ON  L57 AND (HBV OR HBX)
L110(         8)SEA FILE=EMBASE ABB=ON  L58 AND (HBV OR HBX)
```

```
L111(        15)SEA FILE=HCAPLUS ABB=ON  L59 AND (HBV OR HBX)
L112(         0)SEA FILE=NTIS ABB=ON  L60 AND (HBV OR HBX)
L113(         7)SEA FILE=ESBIOBASE ABB=ON  L61 AND (HBV OR HBX)
L114(         7)SEA FILE=BIOTECHNO ABB=ON  L62 AND (HBV OR HBX)
L115(         4)SEA FILE=WPIDS ABB=ON  L63 AND (HBV OR HBX)
L116(         8)SEA FILE=CANCERLIT ABB=ON  L64 AND (HBV OR HBX)
L117(        95)SEA L65 AND (HBV OR HBX)
L118(         0)SEA FILE=SCISEARCH RAN=(2002,) ABB=ON  (L28 OR L41 OR L93 OR L1
L119(         0)SEA FILE=LIFESCI RAN=(2002,) ABB=ON  (L29 OR L42 OR L94 OR L107
L120(         0)SEA FILE=BIOTECHDS RAN=(2002,) ABB=ON  (L30 OR L43 OR L95 OR L1
L121(         0)SEA FILE=BIOSIS RAN=(2002,) ABB=ON  (L31 OR L44 OR L96 OR L109)
L122(         0)SEA FILE=EMBASE RAN=(2002,) ABB=ON  (L32 OR L45 OR L97 OR L110)
L123(         0)SEA FILE=HCAPLUS RAN=(2002,) ABB=ON  (L33 OR L46 OR L98 OR L111
L124(         0)SEA FILE=NTIS RAN=(2002,) ABB=ON  (L34 OR L47 OR L99 OR L112) A
L125(         0)SEA FILE=ESBIOBASE RAN=(2002,) ABB=ON  (L35 OR L48 OR L100 OR L
L126(        46)SEA FILE=BIOTECHNO RAN=(2002,) ABB=ON  (L36 OR L49 OR L101 OR L
L127(         0)SEA FILE=WPIDS RAN=(2002,) ABB=ON  (L37 OR L50 OR L102 OR L115)
L128(         4)SEA FILE=CANCERLIT RAN=(2002,) ABB=ON  (L38 OR L51 OR L103 OR L
L129(        50)SEA (L39 OR L52 OR L104 OR L117) AND PY=<1998
L130         46 DUP REM L129 (4 DUPLICATES REMOVED)

=> d ab 10,11
```

L130 ANSWER 10 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.

AB The hepatitis B virus and the mammalian hepadnavirus genomes encode for a short open reading frame called x. Expression of the protein product (**HBx**) appears necessary for establishment of natural infection. However, in vitro studies have suggested a multifunctional role for **HBx** as an indirect transcriptional transactivator of a variety of different viral and cellular promoters. Indeed, **HBx** has no known direct DNA binding properties but may interact with transcription factors as well as activate intracellular signaling pathways associated with cell growth. To further address the possible functional role of **HBx** in the life cycle of hepatitis B virus, we performed an analysis using the yeast two-hybrid system to screen a cDNA library derived from a hepatocellular carcinoma cell line with a **HBx** fusion bait in an attempt to identify cellular partners that may bind to and alter the biologic properties of **HBx**. A **HBx** -interacting protein that specifically complexes with the carboxy terminus of wild-type **HBx** was identified and designated XIP. This 9.6-kDa protein is capable of binding to **HBx** in vitro, and transient and stable expression in hepatocellular carcinoma cells abolishes the transactivation properties of **HBx** on luciferase constructs driven by AP-1 and endogenous hepatitis B virus enhancer/promoter elements. Investigation of the role of XIP in hepatitis B virus replication in differentiated hepatocellular carcinoma cells revealed that XIP expression reduces wild-type hepatitis B virus replication to levels observed following transfection with an **HBx** -minus virus. In contrast, the replication levels of the duck hepatitis B virus, a hepadnavirus that lacks the x open reading frame, were unchanged in the context of XIP expression. We propose that one of the physiologic functions of the cellular protein XIP is to negatively regulate **HBx** activity and thus to alter the replication life cycle of the virus.

L130 ANSWER 11 OF 46 BIOTECHNO COPYRIGHT 2003 Elsevier Science B.V.

AB Hepatitis B virus is a causative agent of hepatocellular carcinoma, and in the course of tumorigenesis, the X-gene product (**HBx**) is known to play important roles. Here, we investigated the transforming potential of **HBx** by conventional focus formation assay in NIH3T3 cells. Cells were cotransfected with the **HBx** expression plasmid along with other oncogenes including Ha-ras, v-**src**, v-myc, v-fos, and Ela. Unexpectedly, the introduction of **HBx** completely abrogated the focus-forming ability of all five tested

oncogenes. In addition, the cotransfection of Bcl-2, an apoptosis **inhibitor**, reversed the **HBx**-mediated **inhibition** of focus formation, suggesting that the observed repression of focus formation by **HBx** is through the induction of apoptosis. Next, to test unequivocally whether **HBx** induces apoptosis in liver cells, we established stable Chang liver cell lines expressing **HBx** under the control of a tetracycline-inducible promoter. Induction of **HBx** in these cells in the presence of 1% calf serum resulted in typical apoptosis phenomena such as DNA fragmentation, nuclear condensation, and fragmentation. Based on these results, we propose that **HBx** sensitizes liver cells to apoptosis upon hepatitis B virus infection, contributing to the development of hepatitis and the subsequent generation of hepatocellular carcinoma.

```
=> s cyclosporin a or csa
FILE 'MEDLINE'
         13449 CYCLOSPORIN
       7168354 A
          9650 CYCLOSPORIN A
                 (CYCLOSPORIN(W)A)
          8595 CSA
L131      15407 CYCLOSPORIN A OR CSA

FILE 'SCISEARCH'
         11822 CYCLOSPORIN
       8763214 A
          8739 CYCLOSPORIN A
                 (CYCLOSPORIN(W)A)
          7688 CSA
L132      14137 CYCLOSPORIN A OR CSA

FILE 'LIFESCI'
          4953 "CYCLOSPORIN"
       1906303 "A"
          4585 CYCLOSPORIN A
                 ("CYCLOSPORIN"(W)"A")
          2663 CSA
L133       5417 CYCLOSPORIN A OR CSA

FILE 'BIOTECHDS'
           258 CYCLOSPORIN
        294014 A
           173 CYCLOSPORIN A
                 (CYCLOSPORIN(W)A)
           118 CSA
L134        285 CYCLOSPORIN A OR CSA

FILE 'BIOSIS'
         18364 CYCLOSPORIN
       7263717 A
          13207 CYCLOSPORIN A
                 (CYCLOSPORIN(W)A)
          8666 CSA
L135      18775 CYCLOSPORIN A OR CSA

FILE 'EMBASE'
         55261 "CYCLOSPORIN"
       6299683 "A"
          32692 CYCLOSPORIN A
                 ("CYCLOSPORIN"(W)"A")
          8449 CSA
L136      36018 CYCLOSPORIN A OR CSA
```

```
FILE 'HCAPLUS'
         13212 CYCLOSPORIN
      17179017 A
         10989 CYCLOSPORIN A
                 (CYCLOSPORIN(W)A)
          6892 CSA
L137      14556 CYCLOSPORIN A OR CSA

FILE 'NTIS'
            33 CYCLOSPORIN
       1626251 A
            20 CYCLOSPORIN A
                 (CYCLOSPORIN(W)A)
           292 CSA
L138        310 CYCLOSPORIN A OR CSA

FILE 'ESBIOBASE'
          4545 CYCLOSPORIN
       1831231 A
          3574 CYCLOSPORIN A
                 (CYCLOSPORIN(W)A)
          3042 CSA
L139      5443 CYCLOSPORIN A OR CSA

FILE 'BIOTECHNO'
          8256 CYCLOSPORIN
       1374224 A
          5655 CYCLOSPORIN A
                 (CYCLOSPORIN(W)A)
          1929 CSA
L140      6226 CYCLOSPORIN A OR CSA

FILE 'WPIDS'
          1232 CYCLOSPORIN A
                 (CYCLOSPORIN)
           256 CSA
L141      1455 CYCLOSPORIN A OR CSA

FILE 'CANCERLIT'
          4063 CYCLOSPORIN
       1400898 A
          3272 CYCLOSPORIN A
                 (CYCLOSPORIN(W)A)
          2574 CSA
L142      4843 CYCLOSPORIN A OR CSA

TOTAL FOR ALL FILES
L143    122872 CYCLOSPORIN A OR CSA

=> s hepatitis b virus or hbv or hbx
FILE 'MEDLINE'
        114472 HEPATITIS
        541713 B
        351997 VIRUS
         18520 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
         11224 HBV
           310 HBX
L144     21340 HEPATITIS B VIRUS OR HBV OR HBX

FILE 'SCISEARCH'
         82452 HEPATITIS
       1017714 B
        301493 VIRUS
```

```
         14176 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
          9354 HBV
           372 HBX
L145      17662 HEPATITIS B VIRUS OR HBV OR HBX

FILE 'LIFESCI'
         20784 "HEPATITIS"
        183440 "B"
        175163 "VIRUS"
          8405 HEPATITIS B VIRUS
                 ("HEPATITIS"(W)"B"(W)"VIRUS")
          4363 HBV
           193 HBX
L146       8719 HEPATITIS B VIRUS OR HBV OR HBX

FILE 'BIOTECHDS'
          3962 HEPATITIS
         41375 B
         39878 VIRUS
          1876 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
           501 HBV
            10 HBX
L147       1896 HEPATITIS B VIRUS OR HBV OR HBX

FILE 'BIOSIS'
         98112 HEPATITIS
        637399 B
        470549 VIRUS
         24464 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
         11588 HBV
           335 HBX
L148      25732 HEPATITIS B VIRUS OR HBV OR HBX

FILE 'EMBASE'
         87026 "HEPATITIS"
        581745 "B"
        382372 "VIRUS"
         18894 HEPATITIS B VIRUS
                 ("HEPATITIS"(W)"B"(W)"VIRUS")
          9566 HBV
           263 HBX
L149      20683 HEPATITIS B VIRUS OR HBV OR HBX

FILE 'HCAPLUS'
         38684 HEPATITIS
       1362645 B
        284236 VIRUS
          9915 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
          5765 HBV
           631 HBX
L150      10720 HEPATITIS B VIRUS OR HBV OR HBX

FILE 'NTIS'
          1201 HEPATITIS
         65826 B
          7315 VIRUS
           123 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
            82 HBV
            26 HBX
```

```
L151       182 HEPATITIS B VIRUS OR HBV OR HBX

FILE 'ESBIOBASE'
         18528 HEPATITIS
        248813 B
         82179 VIRUS
          4060 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
          3290 HBV
           187 HBX
L152       4823 HEPATITIS B VIRUS OR HBV OR HBX

FILE 'BIOTECHNO'
         25714 HEPATITIS
        213079 B
        169733 VIRUS
          7893 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
          4778 HBV
           208 HBX
L153       8502 HEPATITIS B VIRUS OR HBV OR HBX

FILE 'WPIDS'
          9661 HEPATITIS
       1050002 B
         31228 VIRUS
          1249 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
           687 HBV
            12 HBX
L154       1483 HEPATITIS B VIRUS OR HBV OR HBX

FILE 'CANCERLIT'
         21807 HEPATITIS
        140342 B
        121638 VIRUS
          5321 HEPATITIS B VIRUS
                 (HEPATITIS(W)B(W)VIRUS)
          3543 HBV
           188 HBX
L155       6006 HEPATITIS B VIRUS OR HBV OR HBX

TOTAL FOR ALL FILES
L156     127748 HEPATITIS B VIRUS OR HBV OR HBX

=> s l143 and l156
FILE 'MEDLINE'
L157         38 L131 AND L144

FILE 'SCISEARCH'
L158         28 L132 AND L145

FILE 'LIFESCI'
L159          9 L133 AND L146

FILE 'BIOTECHDS'
L160          1 L134 AND L147

FILE 'BIOSIS'
L161         51 L135 AND L148

FILE 'EMBASE'
L162        143 L136 AND L149
```

```
FILE 'HCAPLUS'
L163        13 L137 AND L150

FILE 'NTIS'
L164         0 L138 AND L151

FILE 'ESBIOBASE'
L165        11 L139 AND L152

FILE 'BIOTECHNO'
L166        35 L140 AND L153

FILE 'WPIDS'
L167         4 L141 AND L154

FILE 'CANCERLIT'
L168        15 L142 AND L155

TOTAL FOR ALL FILES
L169       348 L143 AND L156

=> s bapta or cgp37157
FILE 'MEDLINE'
          2279 BAPTA
             9 CGP37157
L170      2288 BAPTA OR CGP37157

FILE 'SCISEARCH'
          2228 BAPTA
             9 CGP37157
L171      2237 BAPTA OR CGP37157

FILE 'LIFESCI'
           771 BAPTA
             5 CGP37157
L172       776 BAPTA OR CGP37157

FILE 'BIOTECHDS'
             4 BAPTA
             0 CGP37157
L173         4 BAPTA OR CGP37157

FILE 'BIOSIS'
          2707 BAPTA
            13 CGP37157
L174      2718 BAPTA OR CGP37157

FILE 'EMBASE'
          2148 BAPTA
             9 CGP37157
L175      2157 BAPTA OR CGP37157

FILE 'HCAPLUS'
          2381 BAPTA
            11 CGP37157
L176      2392 BAPTA OR CGP37157

FILE 'NTIS'
            14 BAPTA
             0 CGP37157
L177        14 BAPTA OR CGP37157

FILE 'ESBIOBASE'
          1504 BAPTA
```

```
            9 CGP37157
L178      1513 BAPTA OR CGP37157

FILE 'BIOTECHNO'
          554 BAPTA
            2 CGP37157
L179      556 BAPTA OR CGP37157

FILE 'WPIDS'
           31 BAPTA
            0 CGP37157
L180       31 BAPTA OR CGP37157

FILE 'CANCERLIT'
          426 BAPTA
            0 CGP37157
L181      426 BAPTA OR CGP37157

TOTAL FOR ALL FILES
L182    15112 BAPTA OR CGP37157

=> s l182 and l156
FILE 'MEDLINE'
L183        0 L170 AND L144

FILE 'SCISEARCH'
L184        0 L171 AND L145

FILE 'LIFESCI'
L185        0 L172 AND L146

FILE 'BIOTECHDS'
L186        0 L173 AND L147

FILE 'BIOSIS'
L187        0 L174 AND L148

FILE 'EMBASE'
L188        0 L175 AND L149

FILE 'HCAPLUS'
L189        0 L176 AND L150

FILE 'NTIS'
L190        0 L177 AND L151

FILE 'ESBIOBASE'
L191        0 L178 AND L152

FILE 'BIOTECHNO'
L192        0 L179 AND L153

FILE 'WPIDS'
L193        0 L180 AND L154

FILE 'CANCERLIT'
L194        0 L181 AND L155

TOTAL FOR ALL FILES
L195        0 L182 AND L156

=> s l169 not 1999-2003/py
FILE 'MEDLINE'
      2232921 1999-2003/PY
```

```
L196        25 L157 NOT 1999-2003/PY

FILE 'SCISEARCH'
       4322983 1999-2003/PY
L197        20 L158 NOT 1999-2003/PY

FILE 'LIFESCI'
        447432 1999-2003/PY
L198         4 L159 NOT 1999-2003/PY

FILE 'BIOTECHDS'
         75902 1999-2003/PY
L199         0 L160 NOT 1999-2003/PY

FILE 'BIOSIS'
       2379802 1999-2003/PY
L200        36 L161 NOT 1999-2003/PY

FILE 'EMBASE'
       1955625 1999-2003/PY
L201        72 L162 NOT 1999-2003/PY

FILE 'HCAPLUS'
       4178726 1999-2003/PY
L202         5 L163 NOT 1999-2003/PY

FILE 'NTIS'
         79420 1999-2003/PY
L203         0 L164 NOT 1999-2003/PY

FILE 'ESBIOBASE'
       1255711 1999-2003/PY
L204         5 L165 NOT 1999-2003/PY

FILE 'BIOTECHNO'
        517931 1999-2003/PY
L205        20 L166 NOT 1999-2003/PY

FILE 'WPIDS'
       3691004 1999-2003/PY
L206         1 L167 NOT 1999-2003/PY

FILE 'CANCERLIT'
        354668 1999-2003/PY
L207        11 L168 NOT 1999-2003/PY

TOTAL FOR ALL FILES
L208       199 L169 NOT 1999-2003/PY

=> dup rem l208
PROCESSING COMPLETED FOR L208
L209       101 DUP REM L208 (98 DUPLICATES REMOVED)

=> d tot

L209 ANSWER 1 OF 101    MEDLINE                          DUPLICATE 1
TI   The hepatitis B virus X protein activates
     nuclear factor of activated T cells (NF-AT) by a cyclosporin
     A-sensitive pathway.
SO   EMBO JOURNAL, (1998 Dec 1) 17 (23) 7066-77.
     Journal code: 8208664. ISSN: 0261-4189.
AU   Lara-Pezzi E; Armesilla A L; Majano P L; Redondo J M; Lopez-Cabrera M
AN   1999059743     MEDLINE
```

L209 ANSWER 2 OF 101 MEDLINE DUPLICATE 2
TI High prevalence of hepatitis G virus (HGV) infection in renal transplantation.
SO NEPHROLOGY, DIALYSIS, TRANSPLANTATION, (1998 Nov) 13 (11) 2909-13.
Journal code: 8706402. ISSN: 0931-0509.
AU Berthoux P; Dejean C; Cecillon S; Batie M; Berthoux F
AN 1999044965 MEDLINE

L209 ANSWER 3 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Distribution of lymphocyte subtypes in liver transplant recipients with viral reinfection or de novo malignancy.
SO Transplantation Proceedings, (1998) 30/5 (1846-1847).
Refs: 5
ISSN: 0041-1345 CODEN: TRPPA8
AU Rayes N.; Bechstein W.O.; Tullius S.G.; Nussler N.C.; Naumann U.; Jonas S.; Neuhaus R.; Serke S.; Neuhaus P.
AN 1998292798 EMBASE

L209 ANSWER 4 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Liver transplantation for end-stage liver disease related to viral hepatitis.
SO Transplantation Proceedings, (1998) 30/5 (1843-1845).
Refs: 4
ISSN: 0041-1345 CODEN: TRPPA8
AU Tisone G.; Angelico M.; Vennarecci G.; Palmieri G.; Orlando G.; Iaria G.; Baiocchi L.; Casciani C.U.
AN 1998292797 EMBASE

L209 ANSWER 5 OF 101 SCISEARCH COPYRIGHT 2003 THOMSON ISI
TI **Cyclosporin A** increases hepatitis B surface antigen production by increased transcription of mRNA in an **hepatitis B virus** transfected cell line.
SO HEPATOLOGY, (OCT 1998) Vol. 28, No. 4, Part 2, Supp. [S], pp. 1691-1691.
Publisher: W B SAUNDERS CO, INDEPENDENCE SQUARE WEST CURTIS CENTER, STE 300, PHILADELPHIA, PA 19106-3399.
ISSN: 0270-9139.
AU Hobbins B L (Reprint); Greer S; Alexander G J M
AN 1998:790700 SCISEARCH

L209 ANSWER 6 OF 101 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Influence of immunosuppression on patient outcome after liver transplantation.
SO Transplantation Proceedings, (June, 1998) Vol. 30, No. 4, pp. 1495-1496.
Meeting Info.: Proceedings of an International Congress on Immunosuppression Orlando, Florida, USA December 11-13, 1997
ISSN: 0041-1345.
AU Mueller, A. R. (1); Platz, K.-P.; Willimski, C.; Berg, T.; Neuhaus, R.; Lobeck, H.; Neuhaus, P.
AN 1998:381099 BIOSIS

L209 ANSWER 7 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 3
TI Effect of partial HLA class I match on acute rejection in viral pre-infected human liver allograft recipients.
SO Transplantation, (27 Apr 1998) 65/8 (1047-1053).
Refs: 59
ISSN: 0041-1337 CODEN: TRPLAU
AU Ontanon J.; Muro M.; Garcia-Alonso A.M.; Minguela A.; Torio A.; Bermejo J.; Pons J.A.; Campos M.; Alvarez-Lopez M.R.
AN 1998151692 EMBASE

L209 ANSWER 8 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 4
TI Improved clinical outcomes with liver transplantation for hepatitis B-induced chronic liver failure using passive immunization.
SO Annals of Surgery, (1998) 227/6 (841-850).

Refs: 24
ISSN: 0003-4932 CODEN: ANSUA5
AU Sawyer R.G.; McGory R.W.; Gaffey M.J.; McCullough C.C.; Shephard B.L.; Houlgrave C.W.; Ryan T.S.; Kuhns M.; McNamara A.; Caldwell S.H.; Abdulkareem A.; Pruett T.L.; Bollinger R.R.; Busuttil R.W.; Gaber O.A.; Klintmalm G.; Diethelm A.G.
AN 1999092827 EMBASE

L209 ANSWER 9 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Reverse seroconversion of hepatitis B after allogeneic bone marrow transplantation: A retrospective study of 37 patients with pretransplant anti-HBs and anti-HBc.
SO Transplantation, (15 Sep 1998) 66/5 (616-619).
Refs: 26
ISSN: 0041-1337 CODEN: TRPLAU
AU Dhedin N.; Douvin C.; Kuentz M.; Saint Marc M.F.; Reman O.; Rieux C.; Bernaudin F.; Norol F.; Cordonnier C.; Bobin D.; Metreau J.-M.; Vernant J.-P.
AN 1998318872 EMBASE

L209 ANSWER 10 OF 101 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI **Cyclosporin A** increases hepatitis B surface antigen production by increased transcription of mRNA in an **hepatitis B virus** transfected cell line.
SO Hepatology, (Oct., 1998) Vol. 28, No. 4 PART 2, pp. 585A.
Meeting Info.: Biennial Scientific Meeting of the International Association for the Study of the Liver and the 49th Annual Meeting and Postgraduate Courses of the American Association for the Study of Liver Diseases Chicago, Illinois, USA November 4-10, 1998 International Association for the Study of the Liver
. ISSN: 0270-9139.
AU Hobbins, Barbara L.; Greer, Shaun; Alexander, Graeme J. M.
AN 1998:526647 BIOSIS

L209 ANSWER 11 OF 101 MEDLINE DUPLICATE 5
TI Antibody to hepatitis B e positive hepatitis induced by withdrawal of steroid therapy for polymyositis: response to interferon-alpha and **cyclosporin A**.
SO INTERNAL MEDICINE, (1998 Jun) 37 (6) 519-22.
Journal code: 9204241. ISSN: 0918-2918.
AU Nakanishi K; Ishikawa M; Nakauchi M; Sakurai A; Doi K; Taniguchi Y
AN 1998341825 MEDLINE

L209 ANSWER 12 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI **Hepatitis B virus** carrier exacerbating fatal hepatitis B following renal transplantation: A case report.
SO Nishinihon Journal of Urology, (1998) 60/3 (223-226).
Refs: 15
ISSN: 0029-0726 CODEN: NHJUAR
AU Sato F.; Imagawa M.; Emoto A.; Nakagawa M.; Nomura Y.
AN 1998123561 EMBASE

L209 ANSWER 13 OF 101 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Indications for liver transplantation.
SO New Zealand Medical Journal, (May 22, 1998) Vol. 111, No. 1066, pp. 177-179.
ISSN: 0028-8446.
AU Gane, Ed; Munn, Stephen
AN 1998:316325 BIOSIS

L209 ANSWER 14 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Hepatitis viruses under immunosuppressive agents.
SO Journal of Gastroenterology and Hepatology, (1998) 13/1 (14-20).
Refs: 75

ISSN: 0815-9319 CODEN: JGHEEO
AU Liaw Y.-F.
AN 1998100304 EMBASE

L209 ANSWER 15 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 6
TI Morbidity and mortality due to liver disease in children undergoing allogeneic bone marrow transplantation: A 10-year prospective study.
SO Blood, (1997) 90/9 (3799-3805).
Refs: 27
ISSN: 0006-4971 CODEN: BLOOAW
AU Locasciulli A.; Testa M.; Valsecchi M.G.; Vecchi L.; Longoni D.; Sparano P.; Rovelli A.; Uderzo C.; Masera G.; Alberti A.
AN 97341256 EMBASE

L209 ANSWER 16 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Outcome of HBs antigen positive kidneys after renal transplantation.
SO Transplantation Proceedings, (1997) 29/5 (2446).
Refs: 4
ISSN: 0041-1345 CODEN: TRPPA8
AU Baron C.T.; Pageaux G.P.; Mourad G.
AN 97268242 EMBASE

L209 ANSWER 17 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 7
TI Efficacy and safety of lamivudine on replication of recurrent hepatitis B after cadaveric renal transplantation.
SO Transplantation, (1997) 64/11 (1624-1627).
Refs: 23
ISSN: 0041-1337 CODEN: TRPLAU
AU Rostaing L.; Henry S.; Cisterne J.-M.; Duffaut M.; Icart J.; Durand D.
AN 1998033009 EMBASE

L209 ANSWER 18 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Alteration of the dismal natural history of fibrosing cholestatic hepatitis secondary to **hepatitis B virus** with the use of lamivudine.
SO Transplantation, (1997) 64/6 (926-928).
Refs: 19
ISSN: 0041-1337 CODEN: TRPLAU
AU Al Faraidy K.; Yoshida E.M.; Davis J.E.; Vartanian R.K.; Anderson F.H.; Steinbrecher U.P.
AN 97303605 EMBASE

L209 ANSWER 19 OF 101 MEDLINE DUPLICATE 8
TI Prevalence of antibodies to hepatitis C virus and correlation with liver disease in renal transplant patients.
SO AMERICAN JOURNAL OF NEPHROLOGY, (1997) 17 (1) 46-52.
Journal code: 8109361. ISSN: 0250-8095.
AU Rostaing L; Izopet J; Cisterne J M; Icart J; Chabannier M H; Panicali H; Durand D
AN 97210924 MEDLINE

L209 ANSWER 20 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Results of kidney transplantation in HBsAG and anti-HCV seropositive renal allograft recipients.
SO Transplantation Proceedings, (1996) 28/6 (3459-3460).
ISSN: 0041-1345 CODEN: TRPPA8
AU Durlik M.; Gaciong Z.; Soluch L.; Rowinska D.; Kozlowska-Boszko B.; Rowinski W.; Szmidt J.
AN 96376840 EMBASE

L209 ANSWER 21 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 9
TI Azathioprine hepatitis in kidney transplant recipients: A predisposing role of chronic viral hepatitis.
SO Transplantation, (1996) 61/12 (1774-1776).

ISSN: 0041-1337 CODEN: TRPLAU
AU Pol S.; Cavalcanti R.; Carnot F.; Legendre C.; Driss F.; Chaix M.-L.; Thervet E.; Chkoff N.; Brechot C.; Berthelot P.; Kreis H.
AN 96220176 EMBASE

L209 ANSWER 22 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI De Novo **hepatitis B virus** infection after orthotopic liver transplantation.
SO Transplantation Proceedings, (1996) 28/3 (1684-1686).
ISSN: 0041-1345 CODEN: TRPPA8
AU Liu P.P.; Chen C.L.; Chen Y.S.; Tai D.I.
AN 96193254 EMBASE

L209 ANSWER 23 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI The long-term course of hepatitis C after kidney transplantation.
SO Transplantation, (1996) 62/10 (1417-1421).
ISSN: 0041-1337 CODEN: TRPLAU
AU Kliem V.; Van den Hoff U.; Brunkhorst R.; Tillmann H.L.; Flik J.; Manns M.P.; Pichlmayr R.; Koch K.M.; Frei U.
AN 96369513 EMBASE

L209 ANSWER 24 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Treatment of chronic hepatitis B and C with alpha interferon in a renal transplant patient.
SO Scandinavian Journal of Urology and Nephrology, (1996) 30/6 (485-487).
ISSN: 0036-5599 CODEN: SJUNAS
AU Rostaing L.; Izopet J.; Cisterne J.-M.; Baron E.; Rumeau J.L.; Chabannier M.-H.; Duffaut M.; Durand D.
AN 97011648 EMBASE

L209 ANSWER 25 OF 101 MEDLINE DUPLICATE 10
TI In vivo CAMPATH-1 followed by T cell-depleted bone marrow transplantation: a potential new mode of therapy for hepatitis-associated severe aplastic anemia (SAA).
SO BONE MARROW TRANSPLANTATION, (1996 Aug) 18 (2) 475-8.
Journal code: 8702459. ISSN: 0268-3369.
AU Nagler A; Ilan Y; Varadi G; Kapelushnik J; Or R
AN 97017852 MEDLINE

L209 ANSWER 26 OF 101 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI **Cyclosporin A** increases hepatitis B surface antigen production in cell culture: A possible mechanisms for fibrosing cholestatic hepatitis.
SO Hepatology, (1996) Vol. 24, No. 4 PART 2, pp. 418A.
Meeting Info.: 47th Annual Meeting and Postgraduate Courses of the American Association for the Study of Liver Diseases Chicago, Illinois, USA November 8-12, 1996
ISSN: 0270-9139.
AU Greer, S.; Howard, J.; Alexander, G. J. M.
AN 1996:558662 BIOSIS

L209 ANSWER 27 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Prospects for antiviral therapy in liver transplantation.
SO International Antiviral News, (1996) 4/8 (157-159).
Refs: 14
ISSN: 0965-2310 CODEN: IANWEL
AU Naoumov N.V.; Williams R.
AN 97014091 EMBASE

L209 ANSWER 28 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 11
TI Pre-core mutants of **hepatitis B virus** in patients receiving immunosuppressive treatment after orthotropic liver transplantation.
SO Journal of Medical Virology, (1996) 50/2 (135-144).

ISSN: 0146-6615 CODEN: JMVIDB
AU Protzer U.; Goergen B.; Hopf U.; Neuhaus P.; Konig V.; Meyer zum Buschenfelde K.-H.; Gerken G.
AN 96345329 EMBASE

L209 ANSWER 29 OF 101 MEDLINE
TI Clinical course of concomitant **Hbv** and Hcv infection in renal allograft recipients.
SO ANNALS OF TRANSPLANTATION, (1996) 1 (2) 11-2.
Journal code: 9802544. ISSN: 1425-9524.
AU Durlik M; Gaciong Z; Soluch L; Rancewicz Z; Rowinska D; Kozlowska-Boszko B; Wyzga J; Walewska-Zielecka B; Rowinski W; Szmidt J; Lao M
AN 1999086746 MEDLINE

L209 ANSWER 30 OF 101 HCAPLUS COPYRIGHT 2003 ACS
TI Synthetic inverso or retro-inverso T-cell epitopes as vaccine
SO PCT Int. Appl., 49 pp.
CODEN: PIXXD2
IN Comis, Alfio; Tyler, Margaret Isabel; Fischer, Peter
AN 1995:994347 HCAPLUS
DN 124:53719

PATENT NO.	KIND	DATE	APPLICATION NO.	DATE
WO 9523166	A1	19950831	WO 1995-AU90	19950224
W: AM, AT, AU, BB, BG, BR, BY, CA, CH, CN, CZ, DE, DK, EE, ES, FI, GB, GE, HU, JP, KE, KG, KP, KR, KZ, LK, LR, LT, LU, LV, MD, MG, MN, MW, MX, NL, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TT, UA				
RW: KE, MW, SD, SZ, UG, AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG				
CA 2183977	AA	19950831	CA 1995-2183977	19950224
AU 9517486	A1	19950911	AU 1995-17486	19950224
AU 699757	B2	19981217		
ZA 9501591	A	19951208	ZA 1995-1591	19950224
EP 751960	A1	19970108	EP 1995-910335	19950224
R: AT, BE, CH, DE, DK, ES, FR, GB, GR, IE, IT, LI, LU, MC, NL, PT, SE				
JP 09509182	T2	19970916	JP 1995-522025	19950224

L209 ANSWER 31 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI [Chronic **hepatitis B virus** infection and acute hepatic failure after renal transplantation].
CHRONISCHE **HBV**-INFEKTION UND LEBERVERSAGEN NACH NIERENTRANSPLANTATION.
SO Schweizerische Medizinische Wochenschrift, (1995) 125/51-52 (2523-2525).
ISSN: 0036-7672 CODEN: SMWOAS
AU Christen R.; Blumberg A.; Pirovino M.
AN 96019170 EMBASE

L209 ANSWER 32 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Vanishing bile duct syndrome after liver transplantation: Alloreactivity or viral reactivity?.
SO Transplantation Proceedings, (1995) 27/4 (2280).
ISSN: 0041-1345 CODEN: TRPPA8
AU Manez R.; Bronsther O.; Kusne S.; Llull R.; Aguado J.M.; Starzl T.E.
AN 95268287 EMBASE

L209 ANSWER 33 OF 101 MEDLINE DUPLICATE 12
TI Fulminant hepatic failure in a renal transplant recipient with positive hepatitis B surface antigens: a case report of fibrosing cholestatic hepatitis.
SO HEPATO-GASTROENTEROLOGY, (1995 Nov-Dec) 42 (6) 913-8.
Journal code: 8007849. ISSN: 0172-6390.
AU Hung Y B; Liang J T; Chu J S; Chen K M; Lee C S

AN 96206598 MEDLINE

L209 ANSWER 34 OF 101 MEDLINE DUPLICATE 13
TI In vitro activation of woodchuck lymphocytes measured by radiopurine incorporation and interleukin-2 production: implications for modeling immunity and therapy in **hepatitis B virus** infection.
SO HEPATOLOGY, (1995 Sep) 22 (3) 687-99.
Journal code: 8302946. ISSN: 0270-9139.
AU Cote P J; Gerin J L
AN 95386105 MEDLINE

L209 ANSWER 35 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Early intragraft inflammatory events of liver allografts leading to chronic rejection.
SO Transplant International, (1995) 8/6 (446-451).
ISSN: 0934-0874 CODEN: TRINE5
AU Lautenschlager I.; Nashan B.; Schlitt H.-J.; Ringe B.; Wonigeit K.; Pichlmayr R.
AN 95315372 EMBASE

L209 ANSWER 36 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI [Long-term therapy after liver transplantation].
LANGZEITBETREUUNG DER PATIENTEN NACH LEBERTRANSPLANTATION.
SO Medizinische Welt, (1995) 46/8-9 (400-404).
ISSN: 0025-8512 CODEN: MEWEAC
AU Oehler G.; Friedrich K.; Vogel H.-M.; Koch H.
AN 95293265 EMBASE

L209 ANSWER 37 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Prevalence and clinical course of hepatitis B and hepatitis C liver disease in ciclosporin-treated renal allograft recipients.
SO Nephron, (1995) 70/4 (397-401).
ISSN: 0028-2766 CODEN: NPRNAY
AU Bang B.K.; Yang C.W.; Yoon S.A.; Kim Y.S.; Chang Y.S.; Yoon Y.S.; Koh Y.B.
AN 95230714 EMBASE

L209 ANSWER 38 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 14
TI Survival after liver transplantation for chronic hepatitis B using reduced immunosuppression.
SO Journal of Hepatology, (1995) 22/3 (257-262).
ISSN: 0168-8278 CODEN: JOHEEC
AU Gish R.G.; Keeffe E.B.; Lim J.; Brooks L.J.; Esquivel C.O.
AN 95096016 EMBASE

L209 ANSWER 39 OF 101 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI A case of orthotopic liver transplantation in Tianjin.
SO Nihon University Journal of Medicine, (1995) Vol. 37, No. 4, pp. 241-247.
ISSN: 0546-0352.
AU Takano, Seigo (1); Takahashi, Tomohide; Miki, Toshio; Oishi, Hitoshi; Tanaka, Kazuhiko; Iwai, Shigetomi; Tanaka, Takashi; Shen, Z. Y.
AN 1995:507575 BIOSIS

L209 ANSWER 40 OF 101 MEDLINE DUPLICATE 15
TI The optimal immunosuppressant after liver transplantation according to diagnosis: cyclosporine A or FK506?.
SO CLINICAL TRANSPLANTATION, (1995 Jun) 9 (3 Pt 1) 176-84.
Journal code: 8710240. ISSN: 0902-0063.
AU Mueller A R; Platz K P; Blumhardt G; Bechstein W O; Steinmuller T; Christe W; Hopf U; Lobeck H; Neuhaus P
AN 96022852 MEDLINE

L209 ANSWER 41 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 16
TI Temporary heterotopic auxiliary liver transplantation for fulminant

hepatitis B.
SO Journal of Hepatology, (1995) 23/2 (109-118).
ISSN: 0168-8278 CODEN: JOHEEC
AU Van Hoek B.; Ringers J.; Kroes A.C.M.; Van Krieken J.H.J.M.; Van Schelven W.D.; Masclee A.A.M.; Van Krikken-Hogenberk L.G.; Haak H.R.; Lamers C.B.H.W.; Terpstra O.T.
AN 95235439 EMBASE

L209 ANSWER 42 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Incidence of new onset diabetes mellitus in liver transplant recipients immunosuppressed with deflazacort.
SO Transplantology: Journal of Cell and Organ Transplantation, (1995) 6/3 (107-115).
Refs: 36
ISSN: 1134-315X CODEN: TANSES
AU Gonzalez-Quintela A.; De la Mata M.; Varo E.; Fraga E.; Montero J.L.; Lopez-Cillero P.; Mino G.; Pera C.
AN 97276102 EMBASE

L209 ANSWER 43 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI [Liver transplantation in patients with posthepatitis D cirrhosis]. TRANSPLANTACAO HEPATICA NA CIRROSE PELO VIRUS DA HEPATITE D.
SO Arquivos de Medicina, (1995) 9/2 (101-108).
ISSN: 0871-3413 CODEN: ARQME3
AU Areias J.; Marcellin P.; Benhamou J.-P.
AN 95184165 EMBASE

L209 ANSWER 44 OF 101 MEDLINE DUPLICATE 17
TI Interferon and **cyclosporin A** in the treatment of fulminant viral hepatitis.
SO JOURNAL OF GASTROENTEROLOGY, (1995 Feb) 30 (1) 67-73.
Journal code: 9430794. ISSN: 0944-1174.
AU Yoshiba M; Sekiyama K; Inoue K; Fujita R
AN 95235716 MEDLINE

L209 ANSWER 45 OF 101 MEDLINE DUPLICATE 18
TI Effect of immunosuppressive and antiviral agents on **hepatitis B virus** replication in vitro.
SO HEPATOLOGY, (1995 Jul) 22 (1) 36-43.
Journal code: 8302946. ISSN: 0270-9139.
AU McMillan J S; Shaw T; Angus P W; Locarnini S A
AN 95324894 MEDLINE

L209 ANSWER 46 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Acute necrotizing pancreatitis due to **hepatitis B virus** reinfection in a liver transplant recipient.
SO Transplantation Proceedings, (1994) 26/6 (3649-3650).
ISSN: 0041-1345 CODEN: TRPPA8
AU Cavallari A.; Vivarelli M.; D'Errico A.; Bellusci R.; Scarani P.; De Raffele E.; Nardo B.; Gozzetti G.
AN 95003306 EMBASE

L209 ANSWER 47 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Clinical and pathologic features of **hepatitis B virus** reinfection after liver transplantation.
SO Transplantation Proceedings, (1994) 26/4 (2263-2264).
ISSN: 0041-1345 CODEN: TRPPA8
AU Jeng L.-B.B.; Ho Y.-C.; Lee W.-C.; Wang C.-C.; Wang K.-L.; Chen S.-C.; Chen - M.F.; Lin D.-Y.; Liaw Y.-F.; Tan P.P.-C.; Chang C.-H.
AN 94261801 EMBASE

L209 ANSWER 48 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Immunoprophylaxis for **hepatitis B virus** reinfection after liver transplantation.

SO Transplantation Proceedings, (1994) 26/4 (2243-2244).
ISSN: 0041-1345 CODEN: TRPPA8
AU Jeng L.-B.B.; Lee W.-C.; Yeh D.-S.; Wang C.-C.; Wang K.-L.; Chen S.-C.; Chen - M.F.; Chien R.-N.; Chiu C.-T.; Lin D.-Y.; Liaw Y.-F.; Tan P.P.-C.; Chang C.-H.
AN 94261791 EMBASE

L209 ANSWER 49 OF 101 MEDLINE DUPLICATE 19
TI Fibrosing cholestatic hepatitis in a hepatitis B surface antigen carrier after renal transplantation.
SO GASTROENTEROLOGY, (1994 Nov) 107 (5) 1514-8.
Journal code: 0374630. ISSN: 0016-5085.
AU Chen C H; Chen P J; Chu J S; Yeh K H; Lai M Y; Chen D S
AN 95011308 MEDLINE

L209 ANSWER 50 OF 101 MEDLINE DUPLICATE 20
TI Fulminant hepatitis following bone marrow transplantation in **hepatitis B virus** carrier siblings.
SO JOURNAL OF GASTROENTEROLOGY, (1994 Oct) 29 (5) 653-5.
Journal code: 9430794. ISSN: 0944-1174.
AU Omata F; Ueno F; Kushibiki Y; Takahashi H
AN 95093592 MEDLINE

L209 ANSWER 51 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 21
TI Long-term follow-up of **hepatitis B virus** -infected recipients after orthotopic liver transplantation.
SO Transplantation, (1994) 58/5 (553-559).
ISSN: 0041-1337 CODEN: TRPLAU
AU Konig V.; Hopf U.; Neuhaus P.; Bauditz J.; Schmidt C.A.; Blumhardt G.; Bechstein W.-O.; Neuhaus R.; Lobeck H.
AN 94288135 EMBASE

L209 ANSWER 52 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 22
TI Impact of immunoprophylaxis and patient selection on outcome of transplantation for HBsAg-positive liver recipients.
SO Journal of Hepatology, (1994) 21/2 (204-210).
ISSN: 0168-8278 CODEN: JOHEEC
AU Devlin J.; Smith H.M.; O'Grady J.G.; Portmann B.; Tan K.C.; Williams R.
AN 94266952 EMBASE

L209 ANSWER 53 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 23
TI Transplantation of a hepatitis B surface antigen-positive donor liver into a **hepatitis B virus**-negative recipient.
SO Transplantation, (1994) 58/1 (114-116).
ISSN: 0041-1337 CODEN: TRPLAU
AU Gonzalez-Peralta R.P.; Andres J.M.; Tung F.Y.; Fang J.W.S.; Brunson M.E.; Davis G.L.; Lau J.Y.N.
AN 94233657 EMBASE

L209 ANSWER 54 OF 101 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC. DUPLICATE 24
TI Recurrent fulminant hepatic failure in an HB carrier after intensive chemotherapy.
SO Digestive Diseases and Sciences, (1993) Vol. 38, No. 9, pp. 1751-1755.
ISSN: 0163-2116.
AU Yoshiba, Makoto (1); Sekiyama, Kazuhiko; Iwabuchi, Shogo; Takatori, Masao; Tanaka, Yasufumi; Uchikoshi, Toshiyuki; Okamoto, Hiroaki; Inoue, Kazuaki; Sugata, Fumio
AN 1993:485940 BIOSIS

L209 ANSWER 55 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Kidney transplantations with HBsAg+ donors.
SO Transplantation Proceedings, (1993) 25/1 SUPPL. 1 (1481-1482).
ISSN: 0041-1345 CODEN: TRPPA8

AU Bedrossian J.; Akposso K.; Metivier F.; Moal M.C.; Pruna A.; Idatte J.M.
AN 93079069 EMBASE

L209 ANSWER 56 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Fatal acute **hepatitis B virus** infection
while receiving immunosuppressants after renal transplantation.
SO Internal Medicine, (1993) 32/7 (547-551).
ISSN: 0918-2918 CODEN: IEDIEP
AU Hamada T.; Kumashiro R.; Koga Y.; Hino T.; Furudera S.; Sakisaka S.; Sata M.; Tanikawa K.; Taguchi J.; Kage M.
AN 93360748 EMBASE

L209 ANSWER 57 OF 101 MEDLINE DUPLICATE 25
TI Pregnancy after liver transplantation.
SO INTERNATIONAL JOURNAL OF GYNAECOLOGY AND OBSTETRICS, (1993 Jun) 41 (3) 273-6.
Journal code: 0210174. ISSN: 0020-7292.
AU Baruch Y; Weiner Z; Enat R; Ronen N; Blumenfeld Z
AN 93365736 MEDLINE

L209 ANSWER 58 OF 101 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI Medical complications of liver transplantation.
SO Digestive Diseases, (1993) Vol. 11, No. 2, pp. 78-101.
ISSN: 0257-2753.
AU Mitchison, H. C. (1); Neuberger, J. M.
AN 1993:463040 BIOSIS

L209 ANSWER 59 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Recurrent hepatitis B in liver allografts: A distinctive form of rapidly developing cirrhosis.
SO Histopathology, (1993) 23/1 (21-28).
ISSN: 0309-0167 CODEN: HISTDD
AU Harrison R.F.; Davies M.H.; Goldin R.D.; Hubscher S.G.
AN 93233262 EMBASE

L209 ANSWER 60 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI [Recurrent hepatitis after liver transplantation: The role of hepatitis B, delta and C viruses].
RECIDIVE EPATITICHE DOPO TRAPIANTO DI FEGATO: RUOLO DEI VIRUS DELL'EPATITE B, DELTA E C.
SO Chirurgia, (1993) 6/1-2 (6-13).
ISSN: 0394-9508 CODEN: CHRRE
AU Cavallari A.; Bellusci R.; De Raffele E.; Miniero R.; Galli S.; Nardo B.; Vivarelli M.; Recordare A.; Conte R.; Grigioni W.; Sprovieri G.; Mazziotti A.; Gozzetti G.
AN 93141029 EMBASE

L209 ANSWER 61 OF 101 WPIDS (C) 2003 THOMSON DERWENT
TI Use of anti-testosterone antibody - for potentiating fundamental immune responses, in treating infectious diseases caused by AIDS, hepatitis, influenza viruses, bacteria, chemotherapy, etc..
PI EP 501320 A1 19920902 (199236)* EN 8p C07K015-00
R: AT BE CH DE DK ES FR GB GR IT LI LU MC NL PT SE
AU 9211030 A 19920827 (199242) A61K039-395
CA 2061405 A 19920827 (199246) A61K039-395
ZA 9201316 A 19921125 (199302) 14p A61K000-00
JP 04356427 A 19921210 (199304) 4p A61K039-395
IN HIRASAWA, K

L209 ANSWER 62 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Renal transplantation is not contraindicated in hepatitis B surface antigen positive patients.
SO Transplantation Proceedings, (1992) 24/4 (1541-1542).
ISSN: 0041-1345 CODEN: TRPPA8

AU Kim Y.S.; Kim S.I.; Suh J.S.; Chon C.Y.; Park K.
AN 92255549 EMBASE

L209 ANSWER 63 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI A case report of living-related kidney transplantation between hepatitis B antigen carriers.
SO Transplantation Proceedings, (1992) 24/4 (1536-1537).
ISSN: 0041-1345 CODEN: TRPPA8
AU Koshizuka S.; Koyama I.; Taguchi Y.; Ogawa N.; Omoto R.
AN 92255547 EMBASE

L209 ANSWER 64 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Reactivation of precore mutant **hepatitis B virus** leading to fulminant hepatic failure following cytotoxic treatment.
SO Digestive Diseases and Sciences, (1992) 37/8 (1253-1259).
ISSN: 0163-2116 CODEN: DDSCDJ
AU Yoshiba M.; Sekiyama K.; Sugata F.; Okamoto H.; Yamamoto K.; Yotsumoto S.
AN 92254348 EMBASE

L209 ANSWER 65 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 26
TI [Risks and prophylaxis of persistent hepatitis B and delta infections after orthotopic liver transplantation].
RISIKEN UND PROPHYLAXE BEI ORTHOTOPER LEBERTRANSPLANTATION UND PERSISTIERENDER INFEKTION MIT HEPATITISVIREN TYP B UND TYP DELTA.
SO Zeitschrift fur Arztliche Fortbildung, (1992) 86/17 (861-868).
ISSN: 0044-2178 CODEN: ZAFBAX
AU Hopf U.; Neuhaus P.; Konig V.; Bauditz J.; Kuther S.; Schmidt A.; Steffen R.; Blumhardt G.; Bechstein W.-O.; Neuhaus C.R.; Lebeck H.; Huhn D.
AN 92300715 EMBASE

L209 ANSWER 66 OF 101 MEDLINE DUPLICATE 27
TI Effect of **cyclosporin-A** in woodchucks with chronic hepatitis delta virus infection.
SO JOURNAL OF MEDICAL VIROLOGY, (1992 Apr) 36 (4) 316-21.
Journal code: 7705876. ISSN: 0146-6615.
AU Karayiannis P; Goldin R; Luther S; Carman W F; Monjardino J; Thomas H C
AN 92251348 MEDLINE

L209 ANSWER 67 OF 101 MEDLINE
TI Factors influencing long-term outcome of living-donor kidney transplantation in the cyclosporine era.
SO CLINICAL TRANSPLANTS, (1992) 257-66.
Journal code: 8812419. ISSN: 0890-9016.
AU Yoon Y S; Bang B K; Jin D C; Ahn S J; Yoon J Y; Park Y H; Koh Y B
AN 93319937 MEDLINE

L209 ANSWER 68 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 28
TI Course of hepatitis B and D virus infection in auxiliary liver grafts in hepatitis b-positive patients. A light-microscopic and immunohistochemical study.
SO Journal of Hepatology, (1992) 14/2-3 (168-175).
ISSN: 0168-8278 CODEN: JOHEEC
AU Ten Kate F.J.W.; Schalm S.W.; Willemse P.J.A.; Blok A.P.R.; Heijtink R.A.; Terpstra O.T.
AN 92110652 EMBASE

L209 ANSWER 69 OF 101 MEDLINE DUPLICATE 29
TI Factors in the development of a liver transplantation programme: experience of 100 consecutive transplantations in Milan's Niguarda Hospital.
SO ITALIAN JOURNAL OF GASTROENTEROLOGY, (1992 Jan) 24 (1) 1-7.
Journal code: 8000544. ISSN: 0392-0623.
AU Bettale G; De Carlis L; Alberti A; Dughetti L; Rizzi P; Rondinara G; Belli

L; Del Favero E; Belli L; Ideo G
AN 92239924 MEDLINE

L209 ANSWER 70 OF 101 MEDLINE DUPLICATE 30
TI **Cyclosporin A** modulates the course of woodchuck hepatitis virus infection and induces chronicity.
SO JOURNAL OF IMMUNOLOGY, (1991 May 1) 146 (9) 3138-44.
Journal code: 2985117R. ISSN: 0022-1767.
AU Cote P J; Korba B E; Steinberg H; Ramirez-Mejia C; Baldwin B; Hornbuckle W E; Tennant B C; Gerin J L
AN 91201884 MEDLINE

L209 ANSWER 71 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Experience with immunoprophylaxis and interferon therapy after liver transplantation in HBsAG positive patients.
SO Transplantation Proceedings, (1991) 23/1 II (1522-1524).
ISSN: 0041-1345 CODEN: TRPPA8
AU Neuhaus P.; Steffen R.; Blumhardt G.; Bechstein W.; Keck H.; Lemmens H.P.; Neuhaus R.; Lobeck H.; Konig V.; Hopf U.
AN 91115704 EMBASE

L209 ANSWER 72 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI **HBV** infection after liver transplantation in HBsAg positive patients: Experience with long-term immunoprophylaxis.
SO Transplantation Proceedings, (1991) 23/1 II (1492-1494).
ISSN: 0041-1345 CODEN: TRPPA8
AU Samuel D.; Bismuth A.; Serres C.; Arulnaden J.L.; Reynes M.; Benhamou J.P.; Brechot C.; Bismuth H.
AN 91115692 EMBASE

L209 ANSWER 73 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Reduced incidence of rejection in patients undergoing liver transplantation for chronic hepatitis B.
SO Transplantation Proceedings, (1991) 23/1 II (1436-1437).
ISSN: 0041-1345 CODEN: TRPPA8
AU Adams D.H.; Hubscher S.G.; Neuberger J.M.; McMaster P.; Elias E.; Buckels J.A.C.
AN 91115671 EMBASE

L209 ANSWER 74 OF 101 MEDLINE DUPLICATE 31
TI Effectiveness of histopathological diagnoses in dysfunction of hepatic transplantation. Review of 146 histopathological studies from 53 transplants.
SO ARCHIVES OF PATHOLOGY AND LABORATORY MEDICINE, (1991 Oct) 115 (10) 998-1005.
Journal code: 7607091. ISSN: 0003-9985.
AU Colina F; Mollejo M; Moreno E; Alberti N; Garcia I; Gomez-Sanz R; Castellano G
AN 91378782 MEDLINE

L209 ANSWER 75 OF 101 SCISEARCH COPYRIGHT 2003 THOMSON ISI
TI EFFECTIVENESS OF HISTOPATHOLOGICAL DIAGNOSES IN DYSFUNCTION OF HEPATIC TRANSPLANTATION - REVIEW OF 146 HISTOPATHOLOGICAL STUDIES FROM 53 TRANSPLANTS
SO ARCHIVES OF PATHOLOGY & LABORATORY MEDICINE, (1991) Vol. 115, No. 10, pp. 998-1005.
AU COLINA F (Reprint); MOLLEJO M; MORENO E; ALBERTI N; GARCIA I; GOMEZSANZ R; CASTELLANO G
AN 91:558163 SCISEARCH

L209 ANSWER 76 OF 101 SCISEARCH COPYRIGHT 2003 THOMSON ISI
TI CHRONIC LIVER DYSFUNCTION IN HEART-TRANSPLANT RECIPIENTS, WITH SPECIAL REFERENCE TO VIRAL-B, VIRAL-C, AND NON-A, NON-B, NON-C HEPATITIS - A RETROSPECTIVE STUDY IN 80 PATIENTS WITH FOLLOW-UP OF 60 MONTHS

SO TRANSPLANTATION, (1991) Vol. 52, No. 4, pp. 645-650.
AU CADRANEL J F (Reprint); GRIPPON P; LUNEL F; DESRUENNES M; LEGER P; AZAR N; MOUSSALLI J; PAUWELS A; CABROL A; SALMON P; LECHARPENTIER Y; CABROL C; HURAUX J M; OPOLON P
AN 91:579499 SCISEARCH

L209 ANSWER 77 OF 101 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI EXPERIENCE WITH QUADRUPLE IMMUNOSUPPRESSION AFTER LIVER TRANSPLANTATION.
SO 26TH MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER, PALMA DE MALLORCA, SPAIN, SEPTEMBER 11-14, 1991. J HEPATOL (AMST). (1991) 13 (SUPPL 2), S97.
CODEN: JOHEEC. ISSN: 0168-8278.
AU BLUMHARDT G; STEFFEN R; KECK H; BECHSTEIN W; RAAKOW R; LOBECK H; TOPALIDIS T; NEUHAUS P
AN 1992:87176 BIOSIS

L209 ANSWER 78 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Infections after heart transplantation.
SO Trasplante - Journal of Organ and Tissue Transplantation, (1991) 2/2 (40-47).
ISSN: 0214-820X CODEN: TOTIEO
AU Herreros J.; Azanza J.; Catalan M.; Llorens R.; Abaya A.R.; Florez I.; Pardo F.J.
AN 91272881 EMBASE

L209 ANSWER 79 OF 101 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI INFLUENCE OF CHRONIC CYTOMEGALOVIRUS AND **HEPATITIS B VIRUS** INFECTIONS ON THE OUTCOME OF RENAL TRANSPLANTATION.
SO FOURTH CONGRESS OF THE EUROPEAN SOCIETY FOR ORGAN TRANSPLANTATION, BARCELONA, SPAIN, NOVEMBER 1-4, 1989. TRANSPLANT PROC. (1990) 22 (4), 1820-1821.
CODEN: TRPPA8. ISSN: 0041-1345.
AU POUTEIL-NOBLE C; CHOSSEGROS P; CAILLETTE A; RAFFAELE P; BOSSHARD S; AYMARD M; TOURAINE J L
AN 1990:509403 BIOSIS

L209 ANSWER 80 OF 101 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI EFFECT OF IMMUNOSUPPRESSIVE DRUGS ON **HEPATITIS B VIRUS HBV** SURFACE ANTIGEN EXPRESSION IN PRIMARY HEPATOCYTE CULTURE.
SO 41ST ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES, CHICAGO, ILLINOIS, USA, NOVEMBER 3-6, 1990. HEPATOLOGY. (1990) 12 (4 PART 2), 861.
CODEN: HPTLD9. ISSN: 0270-9139.
AU LAU J Y N; BAIN V G; SMITH H M; DAVIES S E; TREDGER J M; ALEXANDER G J M; WILLIAMS R
AN 1991:63693 BIOSIS

L209 ANSWER 81 OF 101 MEDLINE DUPLICATE 32
TI Circulating immune complexes in systemic necrotizing vasculitis of the polyarteritis nodosa group. Comparison of **HBV**-related polyarteritis nodosa and Churg Strauss Angiitis.
SO JOURNAL OF AUTOIMMUNITY, (1990 Dec) 3 (6) 789-92.
Journal code: 8812164. ISSN: 0896-8411.
AU Guillevin L; Ronco P; Verroust P
AN 91207603 MEDLINE

L209 ANSWER 82 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Reactivation of **hepatitis B virus** by corticosteroids in a case of idiopathic nephrotic syndrome.
SO Nephron, (1990) 56/2 (224).
ISSN: 0028-2766 CODEN: NPRNAY
AU Rostoker G.; Rosenbaum J.; Maadi A.B.; Nedelec G.; Defoge L.; Vidaud M.; Lang P.; Lagrue G.; Goossens M.; Weil B.

AN 90278112 EMBASE

L209 ANSWER 83 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Infections after auxiliary partial liver transplantation. Experiences in the first ten patients.
SO Infection, (1990) 18/3 (146-151).
ISSN: 0300-8126 CODEN: IFTNAL
AU Van Zeijl J.H.; Kroes A.C.M.; Metselaar H.J.; Willemse P.J.A.; Bruining H.A.; Sluiters J.F.; Schalm S.W.; Terpstra O.T.; Michel M.F.
AN 90186385 EMBASE

L209 ANSWER 84 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 33
TI Liver transplant recipients as a model for the study of HDV infection natural history.
SO Chronic liver damage: proceedings of the Annual Meeting of the Italian National Programme on Liver Cirrhosis. ICS910, (1990) (137-144).
Conference: The Annual Meeting of the Italian National Programme on Liver Cirrhosis, San Miniato, ITALY, 11 JAN 1990 - 13 JAN 1990 Editor: Dianzani M.U.; Gentilini P. Publisher: Elsevier Science Publishers B.V.
ISBN: 0444812113
AU Zignego A.L.; Samuel D.; Dubois F.; Reynes M.; Gentilini P.; Goudeau A.; Benhamou J.P.; Tiollais P.; Bismuth H.; Brechot C.
AN 90238651 EMBASE

L209 ANSWER 85 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Serologic markers of **hepatitis B virus** in kidney transplanted patients and their prognostic significance as an index of chronic liver diseases.
SO Istanbul Tip Fakultesi Mecmuasi, (1990) 53/1 (80-84).
CODEN: TFMEAC
AU Ark E.; Okten A.; Sever M.S.; Aysuna N.; Badur S.; Kocak N.
AN 91078476 EMBASE

L209 ANSWER 86 OF 101 MEDLINE DUPLICATE 34
TI Unusually rapid development of a HBsAG-positive liver cirrhosis after liver transplantation.
SO KLINISCHE WOCHENSCHRIFT, (1989 Oct 17) 67 (20) 1061-5.
Journal code: 2985205R. ISSN: 0023-2173.
AU Lautz H U; Muller R; Wittekind C; Mauz S; Barg-Hock H; Ringe B; Pichlmayr R; Schmidt F W
AN 90065465 MEDLINE

L209 ANSWER 87 OF 101 MEDLINE
TI Renal transplantation in hepatitis B carriers: comparison of azathioprine- and cyclosporine-treated recipients.
SO CLINICAL TRANSPLANTS, (1989) 281-6.
Journal code: 8812419. ISSN: 0890-9016.
AU Lai M K; Huang C C; Chu S H; Chuang C K; Fong M T
AN 91137328 MEDLINE

L209 ANSWER 88 OF 101 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI VIRAL INFECTIONS IN ORGAN TRANSPLANTATION.
SO GARACI, E., ET AL. (ED.). SERONO SYMPOSIA PUBLICATIONS FROM RAVEN PRESS, VOL. 61. MICROBIOLOGICAL, CHEMOTHERAPEUTICAL AND IMMUNOLOGICAL PROBLEMS IN HIGH RISK PATIENTS; 4TH INTERNATIONAL SYMPOSIUM ON CLINICAL MICROBIOLOGY, MARCH 29-APRIL 1, 1989. XVI+310P. RAVEN PRESS: NEW YORK, NEW YORK, USA. ILLUS. (1989) 0 (0), 261-268.
CODEN: SPRPDU. ISSN: 0733-897X. ISBN: 0-88167-622-5.
AU MANCINI C; LUN M T; GAETA A; NAZZARI C; LORINO G; FILADORO F
AN 1990:210411 BIOSIS

L209 ANSWER 89 OF 101 MEDLINE DUPLICATE 35
TI An association between hepatitis-B antigen-negative infantile papular acrodermatitis and Epstein-Barr virus infection.

SO HOKKAIDO IGAKU ZASSHI. HOKKAIDO JOURNAL OF MEDICAL SCIENCE, (1989 Mar) 64 (2) 125-38.
Journal code: 17410290R. ISSN: 0367-6102.
AU Konno M
AN 89277248 MEDLINE

L209 ANSWER 90 OF 101 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI **HBV** CLEARANCE WITHOUT SIGNIFICANT LIVER DISEASE CAN BE OBSERVED AFTER KIDNEY TRANSPLANTATION.
SO 39TH ANNUAL MEETING AND POSTGRADUATE COURSE OF THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES, CHICAGO, ILLINOIS, USA, NOVEMBER 5-8, 1988. HEPATOLOGY (BALTIMORE). (1988) 8 (5), 1324.
CODEN: HPTLD9. ISSN: 0270-9139.
AU CHOSSEGROS P; LEFRANCOIS N; LAFONT S; PICHOUD C; CHEVALLIER P; REVILLARD J P; TOURAINE J L; TREPO C
AN 1989:23900 BIOSIS

L209 ANSWER 91 OF 101 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI FULMINANT HEPATITIS DUE TO REACTIVATION OF CHRONIC **HEPATITIS B VIRUS** INFECTION AFTER ALLOGENEIC BONE MARROW TRANSPLANTATION.
SO Dig. Dis. Sci., (1988) 33 (9), 1185-1191.
CODEN: DDSCDJ. ISSN: 0163-2116.
AU PARIENTE E A; GOUDEAU A; DUBOIS F; DEGOTT C; GLUCKMAN E; DEVERGIE A; BRECHOT C; SCHENMETZLER C; BERNUAU J
AN 1988:491093 BIOSIS

L209 ANSWER 92 OF 101 MEDLINE DUPLICATE 36
TI Prevalence and causes of long-lasting hepatic dysfunction after heart transplantation: a series of 80 patients.
SO ARTIFICIAL ORGANS, (1988 Jun) 12 (3) 234-8.
Journal code: 7802778. ISSN: 0160-564X.
AU Cadranel J F; Grippon P; Mattei M F; Lunel F; Pauwels A; Rossant P; Karkouche B; Cabrol A; Chomette G; Cabrol C; +
AN 88268458 MEDLINE

L209 ANSWER 93 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
TI Liver transplantation in patients with B viral hepatitis and delta infection.
SO Transplantation Proceedings, (1987) 19/5 (4073-4076).
ISSN: 0041-1345 CODEN: TRPPA8
AU Colledan M.; Gislon M.; Doglia M.; Fassati L.R.; Ferla G.; Gridelli B.; Rossi G.; Galmarini D.
AN 88023890 EMBASE

L209 ANSWER 94 OF 101 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI LONG TERM 10-20 YEARS FOLLOW UP OF **HBV** REPLICATION IN KIDNEY ALLOGRAFT RECIPIENTS.
SO 38TH ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR THE STUDY OF LIVER DISEASES, CHICAGO, ILLINOIS, USA, OCTOBER 25-28, 1987. HEPATOLOGY (BALTIMORE). (1987) 7 (5), 1097.
CODEN: HPTLD9. ISSN: 0270-9139.
AU CHOSSEGROS P; LEFRANCOIS N; LAFONT S; PICHOUD C; CHEVALLIER P; REVILLARD J P; TOURAINE J L; TREPO C
AN 1988:63550 BIOSIS

L209 ANSWER 95 OF 101 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI BONE GRAFTING AND INFECTION TRANSMISSION HEPATITIS HIV.
SO Hyg. Med., (1987) 12 (9), 342-343.
CODEN: HYMEDG.
AU SCHEIERMANN N
AN 1988:120358 BIOSIS

L209 ANSWER 96 OF 101 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

TI **HBV** CLEARANCE CAN BE OBSERVED IN RENAL ALLOGRAFT RECIPIENTS DESPITE IMMUNOSUPPRESSION DISCREPANCIES BETWEEN **HBV** SEROLOGY AND DNA ARE FREQUENT.
SO 22ND MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER, TORINO, ITALY, SEPTEMBER 3-5, 1987. J HEPATOL (AMST). (1987) 5 (SUPPL 1), S111.
CODEN: JOHEEC.
AU CHOSSEGROS P; LEFRANCOIS N; PICHOUD C; CHEVALLIER P; TOURAINE J L; TREPO C
AN 1988:62544 BIOSIS

L209 ANSWER 97 OF 101 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI LIVER DYSFUNCTION IN HEART TRANSPLANT RECIPIENTS.
SO 22ND MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER, TORINO, ITALY, SEPTEMBER 3-5, 1987. J HEPATOL (AMST). (1987) 5 (SUPPL 1), S102.
CODEN: JOHEEC.
AU CADRANEL J F; GRIPPON P; MATTEI M F; ROSSANT J M; LUNEL F; KARKOUCHE B; CABROL A; CABROL C; OPOLON P
AN 1988:62526 BIOSIS

L209 ANSWER 98 OF 101 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.
TI CRITICAL EVALUATION OF AUTOLOGOUS CYTOTOXICITY IN **HBV** CHRONIC HEPATITIS IN-VIVO AND IN-VITRO.
SO 22ND MEETING OF THE EUROPEAN ASSOCIATION FOR THE STUDY OF THE LIVER, TORINO, ITALY, SEPTEMBER 3-5, 1987. J HEPATOL (AMST). (1987) 5 (SUPPL 1), S55.
CODEN: JOHEEC.
AU ROBAEYS G; FEVERY J; VANDEPUTTE M; DE GROOTE J
AN 1988:62439 BIOSIS

L209 ANSWER 99 OF 101 SCISEARCH COPYRIGHT 2003 THOMSON ISI
TI VACCINATION AGAINST **HEPATITIS-B VIRUS** IN RENAL-TRANSPLANT RECIPIENTS - A COMPARATIVE-STUDY BETWEEN PATIENTS (PTS) TREATED WITH AZATHIOPRIN/STEROIDS AND CYCLOSPORINE-A (**CSA**) MONOTHERAPY
SO KIDNEY INTERNATIONAL, (1986) Vol. 30, No. 3, pp. 453.
AU HUSER B (Reprint); FROSNER G; LANDMANN J; THIEL G
AN 86:486386 SCISEARCH

L209 ANSWER 100 OF 101 MEDLINE DUPLICATE 37
TI T cell subsets in patients with acute and chronic **HBV** infection, primary biliary cirrhosis and alcohol induced liver disease.
SO INTERNATIONAL JOURNAL OF IMMUNOPHARMACOLOGY, (1981) 3 (3) 301-5.
Journal code: 7904799. ISSN: 0192-0561.
AU Thomas H C
AN 82029865 MEDLINE

L209 ANSWER 101 OF 101 LIFESCI COPYRIGHT 2003 CSA
TI Hepatitis B and Herpes Viral Components in the Cerebrospinal Fluid of Chronic Schizophrenic and Senile Demented Patients.
SO ACTA VIROL. (ENGL. ED.)., (1981) vol. 25, no. 4, pp. 182-190.
AU Libikova, H.; Pogady, J.; Stancek, D.; Mucha, V.
AN 81:13511 LIFESCI

=>
=> d ab
14,22,27,29,31,33,36-38,40,44,45,47,48,50,51,53,56,59,60,67,68,70,72,73,76,87,88

L209 ANSWER 14 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AB Clinical and experimental studies have shown that T cell-mediated immune mechanisms are involved in the pathogenesis of **hepatitis B virus** (**HBV**) and hepatitis C virus infection. Immunosuppressions may impair T cell function and thereby reduce

immune-mediated hepatocytolysis and virus clearance. In addition, corticosteroid may activate the glucocorticoid responsive element in the **HBV** genome to enhance **HBV** replication and gene expression. These combined effects result in an increase of viraemia in association with a decrease of serum aminotransferase and hepatic necroinflammation. In acute infection, use of immunosuppressants will increase the incidence of chronic evolution. In chronic infection, withdrawal of immunosuppressants will be followed by a clinical flare due to a rebound of immune attack to hepatocytes with increased viral load. This may lead to a subsequent decrease of the viraemia. Therefore, short-term use of immunosuppressant before antiviral therapy may be beneficial in the treatment of chronic viral hepatitis. However, the clinical rebound may be extremely severe and lead to hepatitis failure; thus, the patients should be monitored closely upon tapering and after the withdrawal of immunosuppressants. Long-term use of immunosuppressants in patients with hepatitis virus infection is usually deleterious, particularly in patients after organ transplantation. These findings suggest that clinicians should be cautious in the use of immunosuppressants in patients with hepatitis virus infection.

L209 ANSWER 22 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

L209 ANSWER 27 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

L209 ANSWER 29 OF 101 MEDLINE

AB We evaluated the impact of concomitant infection with **Hepatitis B virus** (**HBV**) and Hepatitis C virus (HCV) on the clinical course after renal transplantation (Tx). In 335 patients (pts) transplanted between 1991 and 1993 we found 30 (9%) recipients who were positive for Hepatitis B surface antigen (HBsAg) (ELISA, Organon) and anti-HCV antibodies (immunoblot assay Lia Tek) preTx. Chronic liver disease (CLD) (two-fold or greater increase in serum ALT and AST levels for at least six months) developed in 40.7% coinfected pts as compared to 24.4% and 25.7% pts infected only with HCV or **HBV**, respectively. Maintenance immunosuppression consisted of P + Aza + **CsA**, mean follow-up time was 28 +/- 15 months. The mean time of the onset of CLD was 3.0 months (range: 1-18 months) after Tx. Percutaneous liver biopsy performed in 5 CLD pts revealed chronic active hepatitis (CAH) in 4 and chronic persistent hepatitis (CPH) in 1 pt. Four pts who had CAH and were positive for HCV RNA (RT PCR) in serum and for HBcAg in liver tissue, received interferon-alpha therapy for 6 months. Clinical improvement of liver function was observed in all of them, but none cleared HBsAg or HCV RNA. One pt lost his graft due to acute rejection. Concomitant infection with **HBV** and HCV is associated with the high risk of development of CLD early after Tx. We recommend that pretransplant evaluation of both anti-HCV and HBsAg positive pts should include liver biopsy to exclude potential recipients with CAH.

L209 ANSWER 31 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

AB Chronic liver diseases, especially due to chronic **hepatitis B virus** infection, are among the leading causes of late mortality in renal transplant recipients. We report on 4 HBsAg-positive patients observed over a period of 8 years, who were free of symptomatic liver disease for 7-19 years after renal transplantation and died within a few days of acute hepatic failure. The cases presented document the prognostic relevance of chronic **hepatitis B virus** infection in renal transplant recipients and illustrate that an asymptomatic HBsAg carrier state can evolve within a very short time to fatal liver disease.

L209 ANSWER 33 OF 101 MEDLINE DUPLICATE 12

AB This 28-year-old male, a **hepatitis B virus** (**HBV**) carrier, received cadaveric renal transplantation and was maintained on **cyclosporin A** and prednisolone.

Jaundice occurred 8 months after the transplantation and he died 2 weeks later due to hepatic failure. The liver histologic findings were compatible with fibrosing cholestatic hepatitis (FCH), which is caused by **HBV** and has only been reported in liver allografts of orthotopic liver transplantations. This is the first case of FCH developing in a renal transplant recipient. The report illustrates that (1) FCH is also a unique histologic entity in renal transplantations; (2) FCH might occur in a liver chronically infected by **HBV** without co-existing hepatitis D virus; and (3) FCH can cause fulminant hepatic failure within one year after transplantation while the patient is still in an immunosuppressed state.

L209 ANSWER 36 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AB The success of a liver transplant may be jeopardised by many complications. 70% of acute organ rejections and 50% of serious infections occur within the first three weeks of surgery. The consequences of **HBV** or HBC virus reinfection or the undesirable effects of immunosuppressive drugs (nephrotoxicity, hypertension and diabetes mellitus) are often not seen until the rehabilitation phase, i.e. the 6th to 12th postoperative weeks. Ultrasonography may be used for evaluating seromas, biliomas, haematomas and vascular complications. During this phase strictures of bile ducts also occasionally occur which necessitate therapeutic intervention. The patient must be fully informed about the need for follow-up investigations to monitor the intensity of immunosuppression. It has not yet been clarified whether immunosuppressive therapy may eventually be withdrawn for those few patients who develop immunotolerance after liver transplantation.

L209 ANSWER 37 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AB We performed this study to evaluate prevalence and clinical course of hepatitis B surface antigen (HBsAg)-positive and anti-hepatitis C virus (HCV)-positive renal transplant recipients. HBsAg positivity was 13.7 and anti-HCV positivity 12.8%. Before transplantation, the HBsAg positivity was observed in 83.5% of the patients, and 16.4% of the patients acquired HBsAg after renal transplantation. In the HCV group, anti-HCV positivity was observed in 47.1% before transplantation, and 19.6% acquired anti-HCV after renal transplantation. The prevalence of chronic hepatitis in the **hepatitis B virus** (**HBV**) and in the HCV groups was not different (25.7 vs. 25.5%). Among those with chronic hepatitis in the **HBV** group, 4 cases progressed to fulminant hepatic failure, 1 case progressed to the end-stage liver cirrhosis, and 1 case to hepatocellular carcinoma. However, in the HCV group, no case showed progression of chronic hepatitis. The overall mortality in the **HBV** and HCV groups was 25.3 and 7.8%, respectively ($p = 0.001$). Among 20 fatal cases in the **HBV** group 9, cases were liver disease related, but no liver disease related death occurred in the HCV group. In conclusion, HCV as well as **HBV** infections are quite prevalent and important causes of posttransplant chronic hepatitis, and the clinical course of anti-HCV-positive recipients is less aggressive than that of HBsAg-positive recipients.

L209 ANSWER 38 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 14
AB Background/Aims: Recurrent **hepatitis B virus** infection after liver transplantation performed for chronic hepatitis B with cirrhosis is influenced by a number of factors, including coinfection with the hepatitis D virus, the level of **HBV** replication, and administration of hepatitis B immune globulin. Another potentially important factor in modulating **HBV** infection after liver transplantation is the degree of immunosuppression post-transplant. We reviewed an institutional experience with liver transplantation for chronic hepatitis B and analyzed the impact of using lower doses of corticosteroids on **HBV** reinfection, expression of recurrent **HBV** disease and patient survival. Methods: Of 17 patients undergoing liver transplantation for chronic hepatitis B, 16 patients

received variable doses of hepatitis B immune globulin for up to 6 months. Results: Fifteen of the 16 patients remained HBsAg-negative during hepatitis B immune globulin therapy, but ultimately 13 of the 17 patients had **HBV** reinfection, including 3 of 4 patients with hepatitis D virus coinfection, Long-term survival (82%) of the 17 chronic hepatitis B patients was not different from the survival (75%) of 195 patients transplanted for other indications. Three of 13 patients who were reinfected died from chronic hepatitis B with liver failure. Reinfection did not appear to be related to the pretransplant degree of viral replication. Compared to an age-and sex-matched control group, patients undergoing liver transplantation for chronic hepatitis B received less cumulative intravenous methylprednisolone and oral prednisone, but did not experience a higher rate of graft rejection. Conclusions: We postulate that use of lower doses of corticosteroids after liver transplantation for chronic hepatitis B is safe and not associated with a higher incidence of graft rejection. Moreover, low-dose maintenance prednisone therapy may modify the course of post-transplant **HBV** reinfection by leading to less viral replication, milder **HBV**-related liver disease and better patient survival.

L209 ANSWER 40 OF 101 MEDLINE DUPLICATE 15
AB Since we may soon be able to choose between primarily **CsA**- or FK506-based immunosuppression, it is important to establish the superior immunosuppressive agent for the individual patient. In the present study, 121 patients, 61 randomly assigned to FK506- and 60 assigned to **CsA**-based immunosuppression, were analyzed according to the primary diagnosis for liver transplantation. One-year patient survival was similar in all groups. However, the incidence and severity of acute rejection within the 1st year after transplantation was significantly higher in patients transplanted due to HCV disease who were receiving FK506 (58.8%) compared with those patients receiving **CsA** (27.8%; p < or = 0.05). Furthermore, the incidence of moderate and severe neurotoxicity was significantly higher during the 1st month after LTX in patients transplanted owing to HCV disease treated with FK506 (35.3%) compared with those patients receiving **CsA** (16.7%; p < or = 0.05). Irrespective of the immunosuppressive regimen, the incidence of early postoperative neurotoxicity was significantly lower in patients transplanted owing to **HBV** disease, alcoholic cirrhosis and various other liver diseases summarized than in patients transplanted due to HCV disease receiving FK506 therapy. During the 1st year, the incidence and severity of rejection in patients transplanted due to alcoholic cirrhosis and PBC was significantly lower in patients treated with FK506 (11.1% for both groups) compared with those patients receiving **CsA** (54.5% and 60.0%, respectively; p < or = 0.05. Furthermore, this was accompanied by a lower incidence of toxicity.(ABSTRACT TRUNCATED AT 250 WORDS)

L209 ANSWER 44 OF 101 MEDLINE DUPLICATE 17
AB The prognosis of fulminant hepatitis due to non-A, non-B virus infection and acute reactivation of **hepatitis B virus** in HB carriers is generally poor, and the treatment of choice in Western countries is recognized as liver transplantation. In countries such as Japan where liver transplantation is not readily available, however, these intractable types of fulminant hepatitis have to be treated medically. Based on the assumption that persistent replication of causal viruses and enhanced host immune responses, especially cellular immunity, to eradicate the viruses are the key mechanism in progressive liver cell destruction and the poor prognosis, we attempted a combination treatment with interferon and **cyclosporin A** for these types of fulminant viral hepatitis. Subjects in the present study consisted of 1 patient with acute severe hepatitis without coma and 13 patients with coma (13 with fulminant hepatic failure) due to non-A, non-B virus and acute reactivation of **hepatitis B virus**. The patients were given interferon-beta, 300 x 10(4) U daily, and

cyclosporin A, at an initial dose of 3 mg/kg, with tapering. Fourteen patients with coma received artificial liver support that we devised. The patient with acute severe hepatitis survived, showing histologically remarkable liver regeneration. Eight of the 14 patients with hepatic coma, all of whom were indications for liver transplantation according to the criteria of the King's College group, survived. Decreased transaminase level, increased liver volume, and histological liver regeneration were observed in all the survivors. The combination of interferon and **cyclosporin A** is worth attempting in fulminant hepatitis caused by non-A, non-B virus and acute reactivation of **hepatitis B virus** in HB carriers.

L209 ANSWER 45 OF 101 MEDLINE DUPLICATE 18

AB **Hepatitis B virus (HBV)** DNA-transfected hepatoma cells were incubated with the immunosuppressive agents prednisolone, azathioprine, and **cyclosporin A** (**CsA**) and the antiviral agents ganciclovir and foscarnet to investigate the effects of these compounds on **HBV** replication. Prednisolone and azathioprine increased intracellular viral DNA and RNA levels approximately twofold and fourfold, respectively. Treatment with **CsA** did not alter the levels of viral RNA or DNA. A combination of all three immunosuppressive agents increased the level of intracellular viral DNA eightfold, indicating an additive effect. Incubation of the cells in the presence of foscarnet decreased levels of both single-stranded and relaxed circular viral DNA, and in the presence of ganciclovir decreased the levels of relaxed circular viral DNA, predictable effects from their known mechanism of action. The stimulatory effect on viral replication induced by the combination of immunosuppressive agents was substantially inhibited by ganciclovir-foscarnet treatment. These observations could have implications for the management of recurrent **HBV** infection after liver transplantation.

L209 ANSWER 47 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

L209 ANSWER 48 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

L209 ANSWER 50 OF 101 MEDLINE DUPLICATE 20

AB A 19-year-old male healthy **hepatitis B virus** (**HBV**) carrier developed fulminant hepatitis following allogenic bone marrow transplantation (BMT) from his brother, who was also a healthy **HBV** carrier, during the first complete remission of acute myelogenic leukemia (M1, FAB classification). Serum markers related to both **HBV** and hepatitis C virus (HCV) were elevated during active liver injury when a point mutation in the precore (pre-C) region occurred in the **HBV**. The patient received low-dose interferon alpha (IFN-alpha), while the dose of **cyclosporin A** was tapered; the patient eventually recovered from the liver injury. Fulminant hepatitis due to **HBV** and/or HCV following BMT is rare, and it is considered to have a very poor prognosis. The rationale for the use of low-dose IFN-alpha with **cyclosporin A** (CyA) is discussed.

L209 ANSWER 51 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V. DUPLICATE 21

AB The outcome after OLT was studied in 53 patients with chronic **hepatitis B virus** (**HBV**)* infection, 15 of whom had, in addition, evidence of hepatitis delta virus (HDV) superinfection. Nine of 53 patients received short-term immunoprophylaxis with anti-hepatitis B surface (HBs) hyperimmunoglobulin up to 1 week after OLT and 44 of 53 patients received long-term unlimited immunoprophylaxis. Eight of 9 (89%) patients with short-term immunoprophylaxis showed reactivation of replication with **HBV** DNA in serum > 10 pg/ml independently of the preoperative **HBV** DNA level and HBsAg

reappeared in all cases. Four (44%) patients in this group lost their graft because of fulminant hepatitis or cirrhosis and required retransplantation, and 2 patients (22%) died after reinfection in the second graft. Nineteen of 44 (43%) patients with long-term immunoprophylaxis developed **HBV** values > 10 pg/ml after transplant and 12 of 44 (27%) became HBsAg+ again. Most of them had quantifiable **HBV** DNA levels before OLT. Retransplantation was required in 5 of 44 (11%) patients and 4 of them died after **HBV** recurrence. The frequency of **HBV** reactivation and the development of viral hepatitis after OLT were associated with the preoperative presence of **HBV**, as determined by the molecular hybridization assay. With nested polymerase chain reaction, all 53 patients were **HBV**-DNA+ in the serum before and after OLT, with just one exception, none of the patients with HDV superinfection died, in spite of increased HDV replication after OLT. The data indicate that long-term immunoprophylaxis with anti-HBs hyperimmunoglobulin after OLT improves the prognosis in **HBV**-infected patients. The preoperative detection of **HBV** DNA in serum by molecular hybridization assay is correlated with graft infection and represents a prognostic parameter. The presence of HDV may have a protective effect after OLT.

L209 ANSWER 53 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 23
AB A critically ill, **HBV** seronegative girl who received a liver from a HBsAg+ donor is described. Despite **HBV** Ig prophylaxis, she was seropositive for HBsAg shortly after transplantation. Although the postoperative period was complicated, **HBV**-related problems were not encountered. Liver dysfunction was noted 7 months after transplantation. At that time, she became anti-HBc IgM-positive, with liver histologic findings suggestive of chronic active hepatitis B. The liver function normalized after a reduction of immunosuppressive therapy and introduction of ciprofloxacin. The patient had low level **HBV** replication during the entire follow-up period (**HBV** DNA-positive by PCR only) and sequencing of the virus on 4 occasions revealed only wild-type **HBV**. She subsequently lost serum HBsAg and **HBV** DNA (even by PCR) and has remained well 2 years after transplantation.

L209 ANSWER 56 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

L209 ANSWER 59 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AB Recurrent **hepatitis B virus** (**HBV**) infection in the liver allograft is a significant cause of morbidity and mortality in those transplanted for chronic **HBV** disease. A detailed histological and immunohistochemical study of recurrent **HBV** disease in liver allografts was carried out using archival paraffin-embedded tissue. A total of 34 follow-up liver biopsies from 14 patients transplanted for **HBV** were available for study. In addition to routine stains, sections were stained with antibodies to a range of **HBV**-antigens. Two patients transplanted for acute **HBV** remained free of re-infection. Five of seven patients transplanted for chronic **HBV** disease who were followed-up, developed **HBV**-associated cirrhosis 12-23 months later. Hepatocyte ballooning, high nucleocapsid antigen load, ductular proliferation and immature fibrous tissue characterized this unusual cirrhosis, which developed rapidly from fibrosing cholestatic hepatitis in at least three cases. Death from liver failure supervened quickly in three of the five patients. These findings support the concept that **HBV** infection in the liver allograft can be a different disease from that occurring in the non-transplant setting, and may be related to high antigen load.

L209 ANSWER 60 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.
AB The indication to liver transplantation in patients with severe liver

disease of viral etiology (**HBV**, HDV, HCV) is still controversial because of the high risk of recurrent graft hepatitis. The aim of the study was to evaluate the incidence and the pattern of viral reinfection in a series of 83 patients who received 95 liver transplants at our institution. **HBV** and HDV serum viral markers were determined preoperatively and at regular time intervals after surgery. Anti-HCV antibodies were retrospectively evaluated, using the ELISA and the 4-RIBA tests, on seriated serum samples stored at -20/-30.degree.C. At least two biopsies were available in patients with graft hepatitis. Twenty-two patients were HBsAg positive before OLT; 3 died in the postoperative period, 9 became HBsAg negative and 10 remained HBsAg positive after transplant. Five patients of the last group experienced **HBV** recurrent hepatitis, 4 **HBV**-HDV hepatitis, one developed acute HDV hepatitis. Among pretransplant anti-HCV positive patients, 10 always showed high titres of anti-HCV during a follow-up of at least 6 months: 8 developed chronic graft hepatitis, while 2 have normal liver function tests and histology. Our data confirm the elevated incidence of recurrent viral infection in HBsAg positive patients undergoing OLT, despite active and passive immunization. Also patients with preoperative anti-HCV positivity were at risk of graft reinfection. In these patients, anti-HCV titres should be closely monitored, especially in case of abnormal liver function tests and histology, when a differential diagnosis with rejection is required.

L209 ANSWER 67 OF 101 MEDLINE

AB To evaluate the effect that **CsA** has had on the weight of some factors previously considered influential on kidney graft survival rates in conventionally immunosuppressed recipients, we analyzed patient and graft survival rates for 524 consecutive living-donor first kidney transplants. All patients were transplanted at the Catholic Medical Center between 1984 and 1991 and treated with **CsA**. The data were stratified to reflect differences in a) HLA matching; b) acute graft rejection within 3 months posttransplant; c) donor sources; d) age; e) sex; f) graft number; g) diabetics; h) **HBV** status; i) DST; and j) number of pretransplant transfusions. Overall actuarial 5-year patient and graft survival rates were 86% and 77%. The actuarial 5-year graft survival rates for the HLA-identical, haploidentical, and mismatched groups were 93%, 75% and 80% (p = 0.3858), respectively. The actuarial 5-year graft survival rates in recipients with acute graft rejection (< 3 months) and without acute graft rejection were 55% and 80% (p = 0.0001). The actuarial 5-year graft survival rates for the **HBV**-positive and -negative groups were 55% and 80% (p = 0.0048). The actuarial 5-year graft survival rates according to the number of pretransplant blood transfusions--0, 1-4, and over 5 units groups--were 65%, 80%, and 81% (p = 0.0026), respectively. We conclude that a) acute graft rejection within 3 months, b) **HBV**-positive, and c) pretransplant nontransfusion had a significant negative influence on long-term graft survival, whereas little or no effect was attributable to HLA matching, donor source, age, sex, graft number, diabetes, and DST.

L209 ANSWER 68 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.DUPLICATE 28

AB Four patients who received an auxiliary partial liver graft for decompensated liver cirrhosis due to hepatitis B (**HBV**), associated in two cases with hepatitis D virus (HDV) superinfection, were studied. The sequential appearance of hepatitis B and D antigens in the grafts was investigated in serial liver biopsies by immuno-histochemical methods and compared with the viral antigenic profiles of the host livers. The histological changes in the liver grafts were studied in relation to the viral expression patterns. One week after transplantation, expression of HBsAg was already apparent in two grafts. HBcAg was found in the graft of the only patient with HBcAg in the host liver. HDAg was expressed in the grafts of both patients with HDV superinfection; in one of these cases HDAg was present without HBsAg. At 3 months, viral antigen expression was maximal. Expression of HBsAg and HBcAg in the grafts of the two

HDV-positive patients was, however, less extensive than in the two **HBV**-positive patients. All patients developed a mild lobular hepatitis, histologically demonstrated between the 47th and 107th posttransplantation day. In the two **HBV**-positive, HDV-negative patients, cirrhotic tranformation of the graft occurred within 1 year. In the HDV-positive patients only a mild chronic active hepatitis with slight or moderate fibrosis was observed after 1 year. We conclude that recurrence of **HBV** and HDV infection in auxiliary liver grafts is demonstrable within 1-3 weeks. **HBV** infection in liver grafts may be a rapidly progressive disease. Coinfection with HDV does not aggravate the acute hepatitis and may even suppress the progression of chronic **HBV**.

L209 ANSWER 70 OF 101 MEDLINE DUPLICATE 30
AB Immunosuppression is known to influence the state of chronic **hepatitis B virus** infection, and is thought to increase the risk of developing chronic infection in newly exposed individuals. **Cyclosporin A** (**CsA**), an immunosuppressive agent that inhibits Th cell function, was administered to woodchucks chronically infected with woodchuck hepatitis virus (WHV), and resulted in a decreased severity of chronic hepatitis and an increased viremia during the treatment. Adult woodchucks inoculated with WHV and given **CsA** for 14 wk had increased viremias, decreased acute phase liver injury, and developed chronic infections at a higher rate compared with immunocompetent woodchucks given virus alone (chronicity in seven of seven WHV + **CsA** + vs zero of nine WHV + **CsA**-; p less than 0.001). These results in a relevant animal model of **hepatitis B virus** infection indicate: 1) that liver injury in acute hepadnavirus infections is immune-mediated and not a direct cytopathic effect of virus replication; 2) that Th cells function in the inflammatory response and in the immunologic control of hepadnavirus infection; and 3) that suppression of Th cell function in acute hepadnavirus infection decreases liver injury but alters the outcome of infection in favor of chronicity. These results also suggest continued challenges in the application of **CsA** in liver transplantation for **hepatitis B virus**-induced diseases.

L209 ANSWER 72 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

L209 ANSWER 73 OF 101 EMBASE COPYRIGHT 2003 ELSEVIER SCI. B.V.

L209 ANSWER 76 OF 101 SCISEARCH COPYRIGHT 2003 THOMSON ISI
AB In order to assess the prevalence, causes, and severity of chronic liver dysfunction (LD) in heart transplant patients, 80 transplanted patients followed for 60 months (median; range, 1.5-98 months) were reviewed. Sustained liver dysfunction was found in 50 patients, occurring during the first year after heart transplantation in 42 (84%) of them. Most patients were asymptomatic (80%). Causes for the liver dysfunction included non-A, non-B hepatitis in 16 cases (32%), viral B hepatitis in 13 (26%), delta hepatitis in one (2%), drug-induced hepatitis in six (12%), and cardiac failure in seven (14%). Anti-HCV antibodies were found in 56.2% of patients with non-A, non-B hepatitis and in 22% of patients with **HBV** hepatitis. It was found neither in patients with drug-induced hepatitis cardiac failure nor in patients with normal liver tests. This study outlines a high prevalence of LD (62.5%) in heart transplant patients, the high frequency of viral-related chronic LD (usually of moderate severity), and high incidence of HCV and **HBV** hepatitis.

L209 ANSWER 87 OF 101 MEDLINE
AB Among 137 renal transplant recipients, 53 were treated with an AZA-prednisolone regimen and 84 with a **CsA**-prednisolone regimen. Carriers of **HBV** had an increased risk of hepatic dysfunction. Forty-two recipients were HBsAg positive. HBsAg-positive status indicated 60% chronic hepatic dysfunction over 3.58 +/- 1.28 years of follow-up in

CsA-treated patients and 64.7% over 6.31 +/- 0.99 years in AZA-treated patients. The presence of **HBV** markers did not seem to affect the patient and graft survival rates in both the **CsA**- and AZA-treated patients. However, anti-HBs positive patients had poorer graft survival in AZA-treated cadaveric transplants. Episodes of chronic hepatic dysfunction lead to marked reduction of **CsA** maintenance dosages. We concluded that it was logical to include **HBV** carriers in our kidney transplantation program. However, they should be followed closely for the possibility of hepatic dysfunction, liver cirrhosis, and hepatoma.

L209 ANSWER 88 OF 101 BIOSIS COPYRIGHT 2003 BIOLOGICAL ABSTRACTS INC.

=> d ab 99

L209 ANSWER 99 OF 101 SCISEARCH COPYRIGHT 2003 THOMSON ISI

=> log y

COST IN U.S. DOLLARS	SINCE FILE ENTRY	TOTAL SESSION
FULL ESTIMATED COST	283.71	283.92

STN INTERNATIONAL LOGOFF AT 15:41:26 ON 08 JUL 2003